(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2007 (25.01.2007)

PCT

(10) International Publication Number
WO 2007/011293 A1

(51) International Patent Classification:
C07D 211/46 (2006.01) *A61P 29/00* (2006.01)
A61K 31/4545 (2006.01) *A61P 37/00* (2006.01)
A61P 11/00 (2006.01) *C07C 309/73* (2006.01)
A61P 19/02 (2006.01)

(21) International Application Number:
PCT/SE2006/000893

(22) International Filing Date: 19 July 2006 (19.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0501719-9 21 July 2005 (21.07.2005) SE
0600838-7 13 April 2006 (13.04.2006) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **AUSTIN, Talbir** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **O'SULLIVAN, David** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **PERRY, Matthew** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **SPRINGTHORPE, Brian** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-151 85 Södertälje (SE).

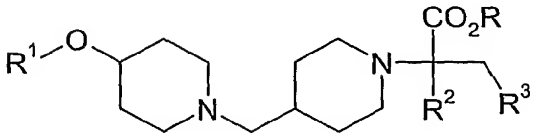
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** NOVEL PIPERIDINE DERIVATIVES



(I)

(57) **Abstract:** The present invention provides a compound of a formula (I): wherein the variables are defined herein; to a process for preparing such a compound; and to the use of such a compound in the treatment of a chemokine (such as CCR3) mediated disease state.

WO 2007/011293 A1

CHEMICAL COMPOUNDS

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO 2004/087659. (2S)-2-[4-[[4-(3,4-Dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid and its dihydrochloride salt are disclosed in WO 2004/087659 (see examples 40 and 73). Compounds of present invention have higher potency at CCR3 than comparable compounds in WO 2004/087659 [which translates to a lower dose meaning less serious side-effects, for example at the IKr channel (for example using the assay described in WO 2005/037052, or the electrophysiology method described in the paper: 'Optimisation and validation of a medium-throughput electrophysiology-based hERG assay using IonWorks™ HT' by M.H. Bridgland-Taylor, C.E. Pollard et al in Journal of Pharmacological and Toxicological Methods (2006; available on the internet Elsevier publications www.sciencedirect.com, and in press))]. The higher potency of the compounds of the invention also translates to increased selectivity over the histamine type 1 (H1) receptor.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of three main types, H1, H2 and H3. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, for example rhinitis or urticaria. H1 antagonists are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and

oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

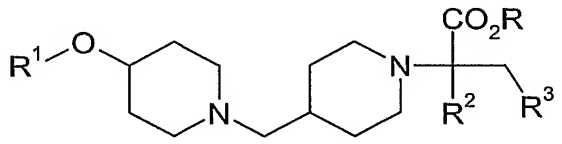
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin, eotaxin-2, eotaxin-3 and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Viral infections are known to cause lung inflammation. It has been shown experimentally that the common cold increases mucosal output of eotaxin in the airways. Instillation of eotaxin into the nose can mimic some of the signs and symptoms of a common cold. (See, Greiff L *et al* Allergy (1999) 54(11) 1204-8 [Experimental common cold increase mucosal output of eotaxin in atopic individuals] and Kawaguchi M *et al* Int.

Arch. Allergy Immunol. (2000) 122 S1 44 [Expression of eotaxin by normal airway epithelial cells after virus A infection].)

The present invention provides a compound of formula (I):



(I)

wherein:

R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl or C_{1-4} alkoxy;

R^2 is methyl or ethyl;

R is hydrogen, or CO_2R is $(CO_2^-)_pR^{p+}$ wherein R^{p+} is a univalent cation (for example an alkali metal cation) or two carboxylates may coordinate a divalent cation (for example an alkaline earth metal cation);

p is 1 or 2;

R^3 is phenyl optionally substituted with halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3;

when R^1 is 2-methyl-3,4-dichlorophenyl and R^3 is 4-fluorophenyl, 4-cyanophenyl or 2-methoxyphenyl, then R^2 can also be hydrogen;

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) wherein R^2 is methyl are surprisingly more soluble (sometimes up to 10 times more soluble) in certain solvents (for example phosphate buffer at pH 7.4) than compounds of formula (I) wherein R^2 is hydrogen. The increased solubility is advantageous for a oral pharmaceutical as the active ingredient will be more readily available for absorption from the gastrointestinal tract.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

The compounds of the invention can be zwitterionic and all such zwitterions are within the invention.

Suitable pharmaceutically acceptable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, fumarate, maleate, malonate, succinate, tartrate, citrate, oxalate, methanesulfonate, benzenesulfonate or *p*-toluenesulfonic acid. $(CO_2^-)_pR^{p+}$ are salts of the invention.

An alkali metal cation is, for example sodium or potassium, and an alkaline earth metal cation is, for example, magnesium or calcium.

The univalent cation R^{p+}, wherein p is 1, can also be, for example, a protonated tertiary amine such as $(CH_2CH_2OH)_3NH^+$.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates. Examples of alternative solvates include compounds of the invention having ethanol or ethyl acetate included in the solid phase. Solvates can exist as, for example, a compound of the invention having solvate molecules within the crystal lattice, or, where solvent is within one or more channels within the crystal lattice (such as a channel hydrate), or a mixture of these two.

Halogen includes fluorine, chlorine, bromine and iodine. Halogen is, for example, fluorine or chlorine.

Alkyl is straight or branched chain and is, for example, methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

In one particular aspect the present invention provides a compound of formula (I) wherein: R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl or C_{1-4} alkoxy; R^2 is methyl; R is hydrogen, or CO_2R is $(CO_2^-)_pR^{p+}$ wherein R^{p+} is a univalent cation (for example an alkali metal cation) or two carboxylates may coordinate a divalent cation (for example an alkaline earth metal cation); p is 1 or 2; R^3 is phenyl optionally substituted with halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3; when R^1 is 2-methyl-3,4-dichlorophenyl and R^3 is 4-fluorophenyl, 4-cyanophenyl or 2-methoxyphenyl, then R^2 can also be hydrogen; or an N-oxide thereof; or a pharmaceutically acceptable salt thereof.

In a further aspect the present invention provides a compound of formula (I) wherein: R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl or C_{1-4} alkoxy; R^2 is methyl; R is hydrogen, or CO_2R is $(CO_2^-)_pR^{p+}$ wherein R^{p+} is a univalent cation (for example an alkali metal cation) or two carboxylates may coordinate a divalent cation (for example an alkaline earth metal cation); p is 1 or 2; R^3 is phenyl optionally substituted with halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3; when R^1 is 2-methyl-3,4-dichlorophenyl and R^3 is 4-fluorophenyl, 4-cyanophenyl or 2-methoxyphenyl, then R^2 can also be hydrogen; or a pharmaceutically acceptable salt thereof.

In another aspect the present invention provides a compound of formula (I) wherein, R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl or C_{1-4} alkoxy; R^2 is

methyl; R is hydrogen, or CO_2R is $(CO_2^-)_pR^{p+}$ wherein R^{p+} is a univalent cation (for example an alkali metal cation) or two carboxylates may coordinate a divalent cation (for example an alkaline earth metal cation); p is 1 or 2; R^3 is phenyl optionally substituted with halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3; or a pharmaceutically acceptable salt thereof.

In a further aspect the present invention provides a compound wherein R^1 is phenyl optionally substituted (for example with two or three of the same or different) with fluorine, chlorine, cyano, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy).

In another aspect the present invention provides a compound wherein R^1 is phenyl optionally substituted (for example with two or three of the same or different) with fluorine, chlorine, cyano or C_{1-4} alkyl (for example methyl).

In yet another aspect the present invention provides a compound wherein R^1 is phenyl substituted by two or three substituents independently selected from: fluorine, chlorine, cyano and methyl.

In a further aspect the present invention provides a compound wherein R^1 is phenyl substituted by two or three substituents independently selected from: chlorine and methyl. For example R^1 is 3,4-dichlorophenyl, 4-chloro-2-methylphenyl, 2,4-dichloro-3-methylphenyl or 3,4-dichloro-2-methylphenyl. R^1 can also be 4-fluoro-2-methylphenyl or 4-chloro-3-methylphenyl. For example R^1 is 3,4-dichloro-2-methylphenyl. For example R^1 is 4-chloro-2-methylphenyl.

In a still further aspect the present invention provides a compound of formula (I) wherein R is hydrogen.

In another aspect the present invention provides a compound of formula (I) wherein CO_2R is $CO_2^-R^+$, wherein R^+ is sodium or potassium.

In yet another aspect R^2 is methyl.

In a still further aspect the present invention provides a compound of formula (I) wherein R^2 is hydrogen and R^3 is 4-fluorophenyl, 4-cyanophenyl or 2-methoxyphenyl (for example R^3 is 4-fluorophenyl).

The invention further provides (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid or a pharmaceutically acceptable salt thereof (for example a sodium, potassium or

$(CH_2CH_2OH)_3NH^+$ salt, or an acid addition salt, such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, fumarate, maleate, malonate, succinate, tartrate, citrate, oxalate, methanesulfonate, benzenesulfonate or *p*-toluenesulfonic acid).

In a still further aspect the present invention provides (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid.

In another aspect the present invention provides a polymorph of (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid hydrate (Form A) {water of varying stoichiometry, for example 1.5-2.5 equivalents} having an X-ray powder diffraction pattern containing specific peaks at: 5.3 (±0.1°), 10.6 (±0.1°), 12.3 (±0.1°), 12.9 (±0.1°), 13.9 (±0.1°), 15.5 (±0.1°), 15.9 (±0.1°), 16.9 (±0.1°), 19.6 (±0.1°), 20.0 (±0.1°), 20.4 (±0.1°), 21.1 (±0.1°), 21.5 (±0.1°), 24.0 (±0.1°), 24.8 (±0.1°), 25.1 (±0.1°), 25.8 (±0.1°), 29.4 (±0.1°) and 29.6 (±0.1°) 2θ.

In yet another aspect the present invention provides a polymorph of (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid ethanol solvate (Form B) having an X-ray powder diffraction pattern containing specific peaks at: 7.7 (±0.1°), 13.3 (±0.1°), 15.2 (±0.1°), 15.4 (±0.1°), 17.4 (±0.1°), 18.4 (±0.1°), 19.7 (±0.1°), 20.6 (±0.1°), 21.7 (±0.1°) and 22.7 (±0.1°) 2θ.

In another aspect the present invention provides a compound wherein R^3 is phenyl optionally substituted with halogen (such as fluoro), cyano or C_{1-4} alkoxy (such as methoxy).

In yet another aspect the present invention provides a compound of formula (I) wherein R^2 is methyl and R^3 is fluorophenyl (for example 4-fluorophenyl).

In another aspect the present invention provides (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid or a pharmaceutically acceptable salt thereof (for example a sodium, potassium or $(CH_2CH_2OH)_3NH^+$ salt, or an acid addition salt, such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, fumarate, maleate, malonate, succinate, tartrate, citrate, oxalate, methanesulfonate, benzenesulfonate or *p*-toluenesulfonic acid).

In yet another aspect the present invention provides (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid.

In a further aspect the present invention provides a polymorph of (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid (Form I) having an X-ray powder diffraction pattern containing specific peaks at: 2.2 (±0.1°), 2.7 (±0.1°), 7.1 (±0.1°), 10.7 (±0.1°), 13.3 (±0.1°) and 18.8 (±0.1°) 2θ.

In a still further aspect the present invention provides a polymorph of (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid (Form II) having an X-ray powder diffraction pattern containing specific peaks at: 2.2 (±0.1°), 2.67 (±0.1°), 7.2 (±0.1°), 13.2 (±0.1°), 17.0 (±0.1°), 17.4 (±0.1°), 19.1 (±0.1°), 19.4 (±0.1°), 21.1 (±0.1°), 24.4 (±0.1°) and 25.2 (±0.1°) 2θ.

In a further aspect the present invention provides a pharmaceutically acceptable salt of a compound of formula (I), having the (2S) absolute configuration, wherein R^1 is 2-methyl-3,4-dichlorophenyl, R^2 is hydrogen and R^3 is phenyl, provided it is not the dihydrochloride salt; such as a methanesulfonate or benzenesulfonate salt.

In another aspect the present invention provides a salt of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid, but not the dihydrochloride salt, [for example an alkali metal salt (such as a sodium or potassium salt) or an acid addition salt (such as one of those listed above, for example a methanesulfonic acid or benzenesulfonic acid salt)]. In yet another aspect the present invention provides a sodium or potassium (for example a sodium salt) of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid.

In a further aspect the present invention provides one of the following individualised compounds of the invention:

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid;

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(2-methoxyphenyl)-propanoic acid;

(2S)-3-(4-cyanophenyl)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-propanoic acid;

(2S)-2-[4-[[4-(3,4-dichloro-2-ethyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid;

(2S)-2-[4-[[4-(3,4-dichloro-2-ethyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid;

(2*S*)-2-(4-{[4-(3-chloro-4-cyano-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-phenylpropanoic acid;

(2*S*)-2-(4-{[4-(3-chloro-4-cyano-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)propanoic acid;

(2S)-2-[4-[[4-(2,4-dichloro-3-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid;

(2*S*)-2-[4-[[4-(4-chloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid;

(2*S*)-2-[4-[[4-(2,4-dichloro-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid;

(*S*)-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid;

(S)-2-[4-[[4-(4-chloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-2-methyl-propanoic acid;

(S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-2-methyl-propanoic acid;

Isomer 1 of 2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid;

Isomer 2 of 2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid;

2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-2-methyl-3-phenylpropanoic acid;

Isomer 1 of 2-[4-[[4-(3,4-dichlorophenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid;

Isomer 2 of 2-[4-[[4-(3,4-dichlorophenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid;

(±)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid;

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid sodium salt;

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid sodium salt;

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid potassium salt;

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid methanesulfonic acid salt;

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid benzenesufonic acid salt;

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid benzenesulfonic acid salt;

(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid hydrochloride;

2-Benzyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)butanoic acid;

(S)-2-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-phenyl-propionic acid;

(S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid (Form I);

(S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid (form II);

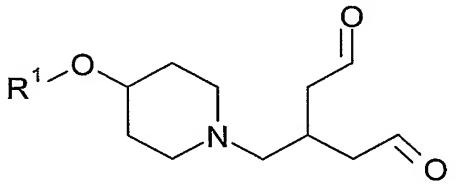
(2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)propanoic acid; or,

(2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-phenylpropanoic acid;

or a pharmaceutically acceptable salt thereof.

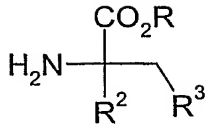
The compounds of the present invention can be prepared as described below or by methods analogous to those described in WO 2004/087659 or WO 2004/029041.

A compound of formula (I) can be prepared by reacting a compound of formula (II):



(II)

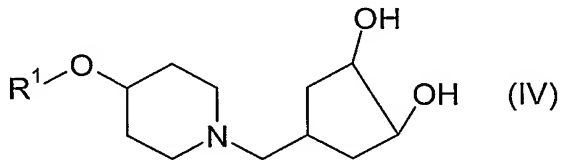
with a compound of formula (III):



(III)

wherein R is alkyl (for example C_{1-6} alkyl) in the presence of $NaBH(OAc)_3$ or $NaBH_3(CN)$ in a suitable solvent (for example an aliphatic alcohol such as methanol or ethanol) at a suitable temperature (such as in the range 0°C to 30°C), and subsequent ester hydrolysis by using or adapting the methods given in the Examples below.

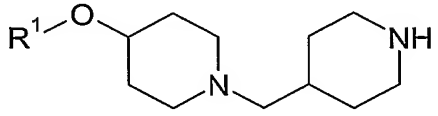
A compound of formula (II) can be prepared by reacting a compound of formula (IV):



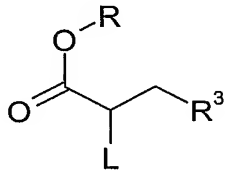
(IV)

with lead tetra-acetate in dichloromethane or sodium periodate in water.

Alternatively a compound of formula (I) wherein R^2 represents H may be prepared by reaction of a compound of formula (V) with a compound of formula (VI)



(V)



(VI)

wherein R is alkyl (for example C_{1-6} alkyl) and L is a suitable leaving group (for example a sulfonate ester, typically triflate or para-nitrobenzenesulfonate), in a suitable solvent, for example dichloromethane or acetonitrile, at a temperature in the range 0 – 30 °C in the presence of a base, for example a tertiary amine, such as triethylamine, or an inorganic base, such as potassium carbonate; and subsequent ester hydrolysis by using or adapting the methods given in the Examples below.

The preparations of various phenoxy piperidines and other intermediates are described in the literature and in WO 01/77101, WO 2004/087659 or WO 2004/029041.

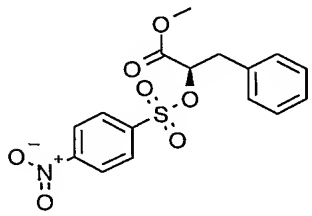
A compound of the present invention wherein R is hydrogen can be prepared by hydrolysis of the corresponding ester (prepared by a method known in the art) under

standard hydrolysis conditions (for example using lithium hydroxide, sodium hydroxide, potassium hydroxide or barium hydroxide).

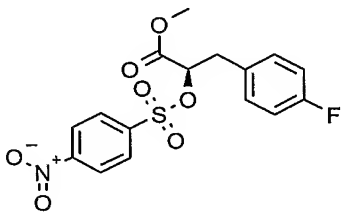
In the above processes it may be desirable or necessary to protect an acid group or a hydroxy or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups may be found in "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

In another aspect the present invention provides processes for the preparation of compounds of formula (I).

In a further aspect the invention provides the intermediates:



(R)-2-(4-nitro-benzenesulfonyloxy)-3-phenyl-propionic acid methyl ester



(R)-3-(4-fluoro-phenyl)-2-(4-nitro-benzene-sulfonyloxy)-propionic acid methyl ester

Salts of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid can be prepared by using or adapting the methods of the Examples or by using or adapting methods known in the art.

The compounds of the invention and their pharmaceutically acceptable salts have activity as pharmaceuticals, in particular as modulators of chemokine receptor (for example CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

Examples of these conditions are:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema;

bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus (RSV), influenza, coronavirus (including SARS) or adenovirus; or eosinophilic esophagitis;

2. bone and joints: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; osteoporosis; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthopathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositits and polymyositis; polymalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthalgias, tendonititides, and myopathies;

3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

5. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial;

6. gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis (including ulcerative colitis, microscopic colitis and indeterminant colitis), proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, irritable bowel disorder, non-inflammatory diarrhoea, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;

8. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

9. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

10. CNS: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumour invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;

11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;

12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;

13. cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins; or,

14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumours and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes.

According to a further feature of the present invention there is provided a method for treating a chemokine mediated disease state (for example a CCR3 mediated disease state) in a mammal, such as man, suffering from, or at risk of, said disease state, which

comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

According to yet another feature of the present invention there is provided a method for treating a sign and/or symptom of what is commonly referred to as a cold in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (for example CCR3 receptor activity) or treating a sign and/or symptom of what is commonly referred to as a cold).

The invention further provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due

to respiratory syncytial virus, influenza, coronavirus (including SARS) or adenovirus; or eosinophilic esophagitis;

2. bone and joints: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; osteoporosis, rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthopathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositits and polymyositis; polymalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthalgias, tendonititides, and myopathies;

3. pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease: arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

4. skin: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid,

epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

5. eyes: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial;

6. gastrointestinal tract: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis (including ulcerative colitis, microscopic colitis and indeterminant colitis), proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, irritable bowel disorder, non-inflammatory diarrhoea, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. abdominal: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;

8. genitourinary: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

9. allograft rejection: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

10. CNS: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumour invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and

peripheral nervous system complications of malignant, infectious or autoimmune processes;

11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;

12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;

13. cardiovascular: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins; or,

14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumours and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes;

in a mammal (for example man).

In a further aspect the invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of the invention, or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

In another aspect a compound of the invention, or a pharmaceutically acceptable salt thereof, is useful in the treatment of respiratory syncytial virus (RSV).

The present invention also provides a the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In order to use a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the therapeutic treatment of a mammal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of of formula (I), or a pharmaceutically acceptable salt thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier.

In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will, for example, comprise from 0.05 to 99 %w (per cent by weight), such as from 0.05 to 80 %w, for example from 0.10 to 70 %w, such as from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral (such as intravenous, sub-cutaneous, intramuscular or intra-articular) administration. For these purposes the compounds of this invention may be formulated by means known in the art. A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

Each patient may receive, for example, a dose of 0.01mgkg^{-1} to 100mgkg^{-1}, for example in the range of 0.1mgkg^{-1} to 20mgkg^{-1}, of the active ingredient administered, for example, 1 to 4 times per day.

The invention further relates to a combination therapy wherein a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically (such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF-α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab;

adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxyfylline.

In addition the invention relates to a combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R) or T-Lymphocytes (such as CTLA4-Ig, HuMax Il-15).

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the C-X_3-C family.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; for example collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyran such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B4, LTC4, LTD4, and LTE4. selected from the group consisting of the phenothiazin-3-y1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and

compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor, an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor antagonist such as cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agent including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist

(including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin (Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir,

ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxyfylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a comP inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitryptiline or other anti-depressant agents, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting

enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) a cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cylin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B.sub1. - or B.sub2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGFβ); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK.sub1. or NK.sub3. receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of p38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; (xxvii) inhibitor of transcription factor activation such as NFkB, API, or STATS; or (xxviii) a non-steroidal glucocorticoid receptor agonist.

In particular a compound of formula (I), or a pharmaceutically acceptable salt thereof, can be combined with a histamine type 1 receptor antagonist such as cetirizine, levocitirizine, loratadine, desloratadine, fexofenadine, acrivistine, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine or mizolastine; applied orally, topically or parenterally (for example orally).

A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

(i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like

5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);

(ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α-reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erb b2 antibody trastuzumab, or the anti-erb b1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin αvβ3 function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;
(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;
(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or,
(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:
(i) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO-D6 (CD_3SOCD_3) or $CDCl_3$ as the solvent unless otherwise stated;
(ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;
(iii) the title and sub-title compounds of the examples and methods were named using either the name program from Advanced Chemistry Development Inc, version 6.00; or the index name program from Ogham with the stereochemical descriptors being added by hand (see www.eyesopen.com/products/applications/ogham.html);
(iv) unless stated otherwise, reverse phase HPLC was conducted using a "Symmetry", "NovaPak" or "Xterra" reverse phase silica column, all available from Waters Corp.;

(v) for analytical HPLC the following conditions were used:

Reverse phase analytical HPLC (Hewlett Packard Series 1100) using Waters "Symmetry" C8 column 3.5μm; 4.6 x 50mm column using 0.1% ammonium acetate/acetonitrile gradients at 2 mL/min given as % aqueous

STANDARD 75% to 5% over 3 min

FAST 45% to 5% over 2.5 min

MEDIUM FAST 65% to 5% in 2.5 min

SLOW 95% to 50% in 2.5 min

SUPERSLOW 100% to 80% in 2.5 min;

(vi) Method for X-Ray Powder Diffractometry (XRPD)

Analyses were performed on a Siemens model D5000 fitted with a position sensitive detector (PSD), a Philips X'pert Pro fitted with an X'celerator detector or a Rigaku MiniFlex X-ray powder diffractometer fitted with a scintillation detector. Samples (1-2mg) were sprinkled on a silicon wafer zero-background holder and irradiated with copper K_α radiation (λ=1.54056Å). Reflections were collected between 2.017 - 39.967°2θ, typically at a step size of 0.033°2θ. Other parameters for these analyses were:

Generator = 45kV 40mA

Scan time ~30min

Measured time/step = 200.025sec

Divergence slit fixed = 1.0

Scan axis = Gonio

PSD length = 2.122

PSD mode = scanning

Incident beam monochromator

Sample = spinning

and

(v) the following abbreviations are used:

RPHPLC	Reverse phase high pressure liquid chromatography
min	minutes
DMEM	tissue culture medium Dulbecco's Modified Eagles Medium
PSG	a combination of penicillin, streptomycin and L-glutamine

FCS	foetal calf serum
NEAA	Non-essential amino acids
h	hour
THF	Tetrahydrofuran
LC/MS	HPLC coupled with mass spectrometry
SCX	Strong cation exchange resin (Isolute SCX-2)

PREPARATION 1

2-Chloro-4-({1-[(3,4-dihydroxycyclopentyl)methyl]piperidin-4-yl}oxy)-3-methylbenzonitrile

A 2-Chloro-4-{[1-(cyclopent-3-en-1-ylmethyl)piperidin-4-yl]oxy}-3-methylbenzonitrile

2-Chloro-3-methyl-4-(piperidin-4-yloxy)benzonitrile (1.3 g) and acetic acid (0.32 ml) were combined in THF (20 ml). Sodium triacetoxyborohydride was added (1.4 g) followed by cyclopent-3-ene-1-carbaldehyde (0.62 g). The reaction was stirred for 1 h and then concentrated. The residue was partitioned between aqueous sodium bicarbonate solution and dichloromethane. The organic phase was washed with brine, dried, filtered and evaporated. The residue was purified by chromatography eluting with ethyl acetate to give the subtitle compound (1.5 g).

^{1}H NMR $\delta_{(CDCl3)}$: 1.78 - 1.90 (2H, m), 1.93 - 2.14 (4H, m), 2.28 - 2.39 (7H, m), 2.41 - 2.53 (3H, m), 2.63 - 2.72 (2H, m), 4.38 - 4.48 (1H, m), 5.64 (2H, s), 6.79 (1H, d), 7.46 (1H, d).

MS (ES+ve) 331/333 (M+H)+

Retention time (standard) 2.66

B 2-Chloro-4-({1-[(3,4-dihydroxycyclopentyl)methyl]piperidin-4-yl}oxy)-3-methylbenzonitrile

2-Chloro-4-(1-cyclopent-3-enylmethyl-piperidin-4-yloxy)-3-methyl-benzonitrile (1.5 g), potassium osmate (vi) dihydrate (0.042 g) and 4-methylmorpholine 4-oxide monohydrate (3.2 ml of a 50% soln in water) were added to acetone (40 ml) and water (5 ml). The reaction mixture was heated under reflux for 1 h. LC/MS showed complete conversion to the desired diol. The reaction was allowed to cool to room temperature and then sodium metabisulfite solution was added. The reaction mixture was extracted with

dichloromethane, then sodium bicarbonate solution was added and the aqueous mixture was extracted again with dichloromethane. The organic extracts were combined and evaporated. The residue was loaded onto an SCX cartridge and eluted with dichloromethane / methanol and then with 0.7M ammonia in methanol to give the title compound (1.3 g).

^{1}H NMR $\delta_{(CDCl3)}$: 1.42 - 1.64 (2H, m), 1.78 - 2.14 (4H, m), 2.23 - 2.47 (9H, m), 2.51 - 2.86 (4H, m), 3.72 (1H, t), 3.92 - 4.18 (2H, m), 4.38 - 4.50 (1H, m), 6.78 (1H, d), 7.46 (1H, d).

MS (ES+ve) 365/367 (M+H)+

Retention time (standard) 1.53

INTERMEDIATE 1

This illustrates the preparation of methyl 2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoate

4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-cyclopentane-1,2-diol (0.50 g) was stirred with acetic acid (0.077 ml) in water until it dissolved. Sodium periodate (0.286 g) was added and the reaction mixture was stirred, under nitrogen, for 15 min. The reaction mixture was neutralised by addition of potassium carbonate (240 mg) and product was extracted with dichloromethane. The dichloromethane was washed with brine, dried ($MgSO_4$), and filtered into a reaction flask containing 2-amino-3-(4-fluoro-phenyl)-propionic acid methyl ester (0.312 g), sodium triacetoxy borohydride (0.651 g) and acetic acid (0.077 ml) in dichloromethane (10 ml). The mixture was strirred at room temperature for 1 h. A saturated solution of sodium bicarbonate was added and product was extracted with dichloromethane. The dichloromethane was washed with brine, dried ($MgSO_4$), filtered and concentrated. Crude product was purified by flash chromatography eluting with ethyl acetate to give the title compound (0.52 g).

^{1}H NMR $\delta_{(CDCL3)}$: 1.08 - 1.29 (m, 2H), 1.41 - 1.63 (m, 1H), 1.69 - 1.86 (m, 4H), 1.90 - 2.00 (m, 2H), 2.14 - 2.39 (m, 9H), 2.57 - 2.68 (m, 2H), 2.82 - 2.95 (m, 2H), 2.97 - 3.09 (m, 2H), 3.39 (dd, 1H), 3.59 (s, 3H), 4.22 - 4.33 (m, 1H), 6.71 (d, 1H), 6.90 - 7.03 (m, 2H), 7.11 - 7.23 (m, 3H).

The following Intermediates were prepared analogously from the appropriate amino esters and diols (diols not previously described were prepared analogously to WO2004087659):

Inter-mediate	Name	MS $[M+H]^+$ (ES+)	Retention time (fast gradient)	^1H NMR $\delta_{(CD3OD)}$
2	Methyl (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(2-methoxyphenyl)-propanoate		2.41	
3	Methyl (2S)-3-(4-cyanophenyl)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-propanoate			0.97 - 1.14 (m, 2H), 1.37 - 1.52 (m, 1H), 1.58 - 1.76 (m, 4H), 1.84 - 1.95 (m, 2H), 2.10 - 2.15 (m, 2H), 2.16 - 2.39 (m, 7H), 2.53 - 2.63 (m, 2H), 2.73 - 2.81 (m, 1H), 2.89 - 2.99 (m, 3H), 3.35 - 3.42 (m, 1H), 3.50 (s, 3H), 4.27 - 4.37 (m, 1H), 6.81 (d, 1H), 7.17 (d, 1H), 7.30 (d, 2H), 7.53 (d, 2H)
4	Methyl (2*S*)-2-(4-{[4-(3,4-dichlorophenoxy)-piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-	537/ 539	2.23	

	2-methylpropanoate			
5	Methyl (2S)-2-[4-[[4-(4-chloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-2-methyl-propanoate	517/ 519	2.20	
6	Methyl (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-2-methyl-propanoate	551/ 553	2.54	
7	(±)-Methyl 2-[4-[[4-(3,4-dichlorophenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoate	519/ 521	2.24	
10	(±)-Methyl 2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoate	533/ 535	2.69	
13	Methyl (2S)-2-[4-[[4-(3,4-dichloro-2-ethyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-	533/ 535	2.66	

	phenylpropanoate			
14	Methyl (2S)-2-[4-[[4-(3,4-dichloro-2-ethyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoate	551/ 553	2.71	
15	Methyl (2*S*)-2-(4-{[4-(3-chloro-4-cyano-2-methylphenoxy)-piperidin-1-yl]methyl}piperidin-1-yl)-3-phenylpropanoate			1.14 - 1.33 (2H, m), 1.50 - 1.65 (1H, m), 1.74 - 1.92 (4H, m), 2.00 - 2.11 (2H, m), 2.24 - 2.30 (3H, m), 2.33 (3H, s), 2.36 - 2.46 (3H, m), 2.64 - 2.74 (2H, m), 2.94 - 3.10 (4H, m), 3.45 (1H, dd), 3.57 (3H, s), 4.58 - 4.66 (1H, m), 7.09 (1H, d), 7.16 - 7.30 (5H, m), 7.61 (1H, d)
16	Methyl (2*S*)-2-(4-{[4-(3-chloro-4-cyano-2-methylphenoxy)-piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)propanoate		2.82 (standard gradient)	1.08 - 1.29 (m, 2H), 1.41 - 1.63 (m, 1H), 1.69 - 1.86 (m, 4H), 1.90 - 2.00 (m, 2H), 2.14 - 2.39 (m, 9H), 2.57 - 2.68 (m, 2H), 2.82 - 2.95 (m, 2H), 2.97 - 3.09 (m, 2H), 3.39 (dd, 1H), 3.59 (s, 3H), 4.22 - 4.33 (m, 1H), 6.71 (d, 1H), 6.90 - 7.03 (m, 2H), 7.11 - 7.23 (m, 3H)
17	Methyl (2*S*)-2-[4-[[4-	537/		1.12 - 1.32 (2H, m), 1.49 -

	(2,4-dichloro-3-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoate	539		1.64 (1H, m), 1.73 - 1.92 (4H, m), 1.95 - 2.06 (2H, m), 2.25 (2H, d), 2.30 - 2.43 (3H, m), 2.47 (3H, s), 2.66 - 2.77 (2H, m), 2.89 - 3.06 (4H, m), 3.42 (1H, dd), 3.58 (3H, s), 3.67 - 3.73 (1H, m), 4.43 - 4.52 (1H, m), 6.94 - 7.07 (3H, m), 7.18 - 7.29 (3H, m)
18	Methyl (2*S*)-2-[4-[[4-(4-chloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoate			1.11 - 1.33 (2H, m), 1.49 - 1.66 (1H, m), 1.73 - 1.88 (4H, m), 1.97 - 2.07 (2H, m), 2.20 (3H, s), 2.23 - 2.28 (3H, m), 2.30 - 2.44 (3H, m), 2.66 - 2.76 (2H, m), 2.91 - 3.08 (4H, m), 3.39 - 3.46 (1H, m), 3.58 (3H, s), 4.36 - 4.44 (1H, m), 6.89 (1H, d), 6.96 - 7.04 (2H, m), 7.07 - 7.14 (2H, m), 7.18 - 7.25 (2H, m)
19	Methyl (2*S*)-2-[4-[[4-(2,4-dichloro-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoate			1.12 - 1.32 (2H, m), 1.49 - 1.64 (1H, m), 1.73 - 1.91 (4H, m), 1.95 - 2.05 (2H, m), 2.22 - 2.28 (2H, m), 2.30 - 2.43 (3H, m), 2.67 - 2.77 (2H, m), 2.90 - 3.07 (4H, m), 3.42 (1H, dd), 3.58 (3H, s), 3.69 - 3.73

				(1H, m), 4.43 - 4.53 (1H, m), 6.96 - 7.11 (3H, m), 7.18 - 7.27 (3H, m), 7.41 (1H, d)

INTERMEDIATES 8 & 9

This illustrates the preparation of the 2 enantiomers of methyl 2-[4-[[4-(3,4-dichlorophenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoate

(±)-Methyl 2-[4-[[4-(3,4-dichlorophenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoate (185 mg) was eluted through a Chiralpak AD HPLC column in ethanol containing 0.1% diethylamine to give two enantiomers.

Isomer 1 (76 mg) retention time (Chiralpak AD 4.6 x 250mm; 0.5 ml/min ethanol) 7.68 min.

Isomer 2 (73 mg) retention time (Chiralpak AD 4.6 x 250mm; 0.5 ml/min ethanol) 9.57 min.

INTERMEDIATES 11 & 12

This illustrates the preparation of the 2 enantiomers of methyl 2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoate

These were prepared following the method of Intermediates 8 & 9 using (±)-methyl 2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoate to give two enantiomers.

Isomer 3 retention time (Chiralpak AD 4.6 x 250mm; 0.5 ml/min ethanol containing 0.1% diethylamine) 12.58 min.

Isomer 4 retention time (Chiralpak AD 4.6 x 250mm; 0.5 ml/min ethanol containing 0.1% diethylamine) 15.76 min.

INTERMEDIATE 20

This illustrates the preparation of methyl 2-benzyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)butanoate

This compound was prepared following the method of Example 1 using 2-amino-2-benzyl-butyric acid methyl ester and 4-[4-(3,4-dichloro-phenoxy)-piperidin-1-ylmethyl]-cyclopentane-1,2-diol.

MS (ESI^+) 533/535 ($M+H^+$)

RT (fast gradient) 2.94 min.

INTERMEDIATE 21

This illustrates the preparation of 4-(3,4-dichloro-2-methyl-phenoxy)-piperidine hydrochloride

4-Hydroxypiperidine (32.5 g) and potassium *tert*-butoxide (62.7 g) were added to a 1 L jacketed vessel. Tetrahydrofuran (275 mL) was added followed by N-methylpyrrolidone (25 mL). 1,2-Dichloro-4-fluoro-3-methylbenzene (50 g) in tetrahydrofuran (100 mL) was then added, followed by tetrahydrofuran (100 mL). The mixture was heated to 67 °C overnight then cooled to 50 °C. Water (250 mL) was added and the mixture was stirred for 10 min at 50 °C. The layers were separated and the heating was removed. The organic layer was washed with twice with 10% w/w brine (250 mL). The organic layer was heated to remove solvent by distillation firstly at atmospheric pressure and then under vacuum (400 mbar) whilst isopropanol (950 mL) was added until the tetrahydrofuran was replaced by isopropanol. The solution was then heated to 50 °C. Hydrogen chloride in isopropanol (5.5M, 125 mL) was added, an exotherm to 60 °C was observed and the solution was cooled to 50 °C. The mixture was cooled from 50 °C to 10 °C over 1 h and then stirred overnight at 10 °C. The product was collected by filtration, washed with isopropanol (50 mL) and dried under vacuum at 40 °C to give 4-(3,4-dichloro-2-methyl-phenoxy)-piperidine hydrochloride as an off-white solid (62.3 g).

^1H NMR $\delta_{(CDCL3)}$ 2.17 (2H, dd), 2.29 - 2.39 (2H, m), 2.34 (3H, s), 3.33 (4H, dd), 4.61 - 4.66 (1H, m), 6.68 (1H, d), 7.25 (1H, d), 9.64 - 9.83 (1H, m).

INTERMEDIATE 22

This illustrates the preparation of 4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester

Acetonitrile (144 mL) and water (336 mL) were added to a mixture of 4-(3,4-dichloro-2-methyl-phenoxy)-piperidine hydrochloride (60 g), 4-(toluene-4-

sulfonyloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester (74.7 g) and potassium carbonate (57.3 g) and the mixture was heated to reflux for 7 h, then cooled over 30 min to 75 °C and held at 75 °C for 14 h, then heated over 30 min to reflux. Acetonitrile (192 mL) was added and then the mixture was cooled to 20 °C over 2 h to give a suspension. The suspension was filtered under vacuum, the filter cake was washed with water (180 mL) and then with acetonitrile (180 mL) and dried under vacuum at 40 °C to give 4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester as a white solid (73.9 g).

^{1}H NMR $\delta_{(CD3OD)}$ 0.99 - 1.12 (2H, m), 1.45 (9H, s), 1.69 - 1.85 (5H, m), 1.95 - 2.04 (2H, m), 2.23 (2H, d), 2.31 (3H, s), 2.32 - 2.40 (2H, m), 2.64 - 2.82 (4H, m), 4.05 (2H, d), 4.38 - 4.46 (1H, m), 6.91 (1H, d), 7.27 (1H, d)

INTERMEDIATE 23

This illustrates the preparation of 4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidine di-benzenesulfonate salt

A suspension of 4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester (120 g) and ethanol (600 mL) were heated to 75 °C to give a solution. Benzenesulfonic acid (70% in water, 144.2 g) in ethanol (120 mL) was added dropwise over 45 min followed by a rinse with ethanol (60 mL). The solution was heated at 75 °C for 1 h and was then cooled to 20 °C over 1 h 45 min. The resultant solid was collected, the filter cake was washed with ethanol (480 mL) then dried under vacuum overnight at 40 °C to give 4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidine di-benzenesulfonate salt as a white solid (161.9 g).

^{1}H NMR $\delta_{(DMSO)}$ 1.3-1.41 (2H, m), 1.89-1.93 (3H, m), 2.02-2.15, (4H, m), 2.25, s and 2.34 (3H, s), 2.83-2.94 (2H, m), 3.06-3.12, (4H, m), 3.28-3.36, (2H, m), 3.45-3.49, (1H, m), 3.58-3.62 (1H, m) 4.5-4.65 and 4.78-4.84 (2 x m, 1H) 7.09 and 7.14 (2 x d, 1H), 7.3-7.37, (6H, m), 7.45 (1H, d); 7.59-7.63 (4H, m), 8.23 (1H, br s), 8.49 (1H, br s), 8.98 (1H, br s).

INTERMEDIATE 24

This illustrates the preparation of (R)-2-(4-nitro-benzenesulfonyloxy)-3-phenyl-propionic acid methyl ester

Toluene (160 mL) was added to (R)-3-phenyllactic acid, methyl ester (20 g) and p-nitrobenzenesulfonyl chloride (25.8 g) to give a clear yellow solution which was cooled to 0 °C. Triethylamine (16.4 mL) was added over 15 min, the mixture was stirred at 3 °C for 2 h and then overnight at room temperature. Water (120 mL) was added and the reaction mixture stirred at RT for 1 h. The layers were separated and the organic layer was washed with water (120 mL). Toluene (20 mL) was added to the resulting organic layer and the solution was heated to remove solvent by distillation under vacuum (60 mbar) to leave 140 mL solvent in the vessel. Isohexane (120 mL) was added at 40 °C and the mixture was stirred at this temperature overnight. The mixture was then cooled to 25 °C over 115 min and was then filtered. The filter cake was washed with toluene (20 mL) and isohexane (20 mL), then dried under vacuum at 40 °C to give (R)-2-(4-nitro-benzenesulfonyloxy)-3-phenyl-propionic acid methyl ester as a cream solid (31.6 g).

^{1}H NMR $\delta_{(CDCl3)}$ 3.0-3.08 (1H, dd), 3.2-3.26 (1H, dd), 3.78 (3H, s), 5.0-5.04 (1H, dd), 7.02-7.06 (2H, m), 7.12-7.2 (3H, m), 7.73-7.78 (2H, d), 8.13-8.18 (2H, d).

INTERMEDIATE 25

This illustrates the preparation of (R)-3-(4-fluoro-phenyl)-2-(4-nitro-benzenesulfonyloxy)-propionic acid methyl ester

(R)-3-(4-Fluorophenyl)-2-hydroxypropionic acid methyl ester (20 g) and 4-nitrobenzenesulfonyl chloride (22.8 g) were dissolved in methylisobutyl ketone (240 mL). The solution was cooled to 0-5 °C and triethylamine (10.74 g) was added dropwise over 15 min. The reaction mixture was stirred at 0-5 °C for 2 hours. Water (80 mL) was added and the mixture heated to 35-40 °C to obtain a clear biphasic solution. The aqueous layer was removed and the organic phase washed successively with dilute hydrochloric acid (1M, 80 mL) and then water at 35-40 °C. The organic phase was concentrated by distillation under reduced pressure at 35-40 °C to a final volume of about 120 mL. To the resulting slurry of the product was added isohexane (120 mL) and the mixture cooled to 0-5 °C for 2 h. The solid was filtered, washed with isohexane (60 mL) and then dried in a vacuum oven at 40 °C under reduced pressure to yield the title compound as a yellow solid (32.64 g).

^{1}H NMR $\delta_{(CDCl3)}$ 3.02-3.10 (1H, dd), 3.18-3.24 (1H, dd), 3.73 (3H, s), 6.85—6.91 (2H, m), 7.03--7.07 (2H, m), 7.86 (2H, d), 8.25 (2H, d).

INTERMEDIATE 26

This illustrates the preparation of (S)-2-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-phenyl-propionic acid methyl ester

Water (90 mL) was added to 4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidine di-benzenesulfonate salt (30 g) to give a suspension. The suspension was stirred at room temperature for 2 min to give a clear solution. Tert-butyl methyl ether (150 mL) was then charged in one portion and the vessel contents were warmed to 30 °C. A solution of 10M Sodium Hydroxide (13.9 g) in water (90 mL) was added over 2 min and the solution was stirred at 30 °C for 10 min then the layers were separated. The organic layer was evaporated to dryness, acetonitrile (100 mL) was added and the evaporation was continued until the volume equalled 80 mL. Acetonitrile (70 mL) was then added and to this solution was added potassium carbonate (7.8 g) followed by a solution of (R)-2-(4-nitro-benzenesulfonyloxy)-3-phenyl-propionic acid methyl ester (16.3 g) in acetonitrile (30 mL). The resulting suspension was heated to 60 °C and held at this temperature overnight. The mixture was cooled to 20 °C then tert-butyl methyl ether (150 mL) was added. The suspension was filtered and the vessel and cake were washed with tert-butyl methyl ether (30 mL). The filtrate was washed with 5% brine (90 mL). The layers were separated and the organic layer was washed with ammonium acetate/acetic acid solution (72 mL; 15 g Ammonium acetate in 1 L 0.5 M aqueous acetic acid) at 25 °C and then warmed to 40 °C whereupon hydrochloric acid (1M, 90 mL) was added. The layers were separated, the organic layer was re-extracted with hydrochloric acid (1M, 30 mL) and then the aqueous phases were combined. Tert-butyl methyl ether (150 mL) and 2M Sodium Hydroxide (90 mL) were added and the mixture stirred at 40 °C for 10 min before the phases were separated. The organic phase was reduced in vacuo to a low volume then ethanol (120 mL) was added and distillation was continued for a short time till some of the ethanol had been removed. Ethanol (5 mL) was added to the residue (volume 90 mL) and the solution seeded with (S)-2-{4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-phenyl-propionic acid methyl ester (50 mg) and the mixture was cooled to 5 °C over 3 h. A colourless solid was collected by filtration, the cake was washed with ethanol (15 mL) and the solid dried under vacuum at 35 °C overnight to give the title compound (16.3 g).

INTERMEDIATE 27

This illustrates the preparation of (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid methyl ester

4-[4-(3,4-Dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidine di-benzenesulfonate salt (40 g) was dissolved in water (120 mL). To the stirred solution was added methyl t-butylether (320 mL), followed by a solution of sodium hydroxide (10M, 22.25 mL) in water (120 mL). The solution was heated at 25-30 °C for 20 minutes. The organic layer was separated from the aqueous and about 200 mL of the solvent was removed by distillation at atmospheric pressure. To the residue was added acetonitrile (200 mL) and further solvent removed by distillation to a final volume of about 240 mL. Karl-Fisher analysis of this solution indicated 0.35%w/w water was present. To this solution of the free base in acetonitrile was added potassium carbonate (10.40 g) and a solution of 3-(4-fluorophenyl)-2-(4-nitrobenzenesulfonyloxy)-propionic acid methyl ester (22.80 g) in acetonitrile (24 mL - prepared by heating the acetonitrile to 35 °C). A small amount of solid residue was washed in with acetonitrile (16 mL). The reaction mixture was heated at 60-65 °C for 16 h, then cooled to room temperature and methyl t-butylether (200 mL) added. After stirring at room temperature for 20 minutes, the precipitated salts were filtered and washed with methyl t-butylether (40 mL). The filtrate was stirred successively with sodium chloride solution (5% w/v in water, 120 mL), ammonium acetate solution (96 mL, 0.2M ammonium acetate in 0.5M aqueous acetic acid solution) and sodium chloride solution (5%w/v, 120 mL), each for 10 minutes. The organic layer was separated and solvent distilled off to a final volume of about 120 mL. To the residue was added acetonitrile (120 mL) and the volume reduced to about 120 mL (the final distillate temperature was 78-80 °C). The residue was diluted with acetonitrile (120 mL). A sample was withdrawn and evaporated and weighed to indicate that this solution contained about 33 g of the title compound in 240 mL of acetonitrile.

^{1}H NMR $\delta_{(CDCl3)}$ 1.18-2.30 (2H, m), 1.4-1.56 (1H, m), 1.74-1.90 (4H, m), 1.90-1.93 (2H, m), 2.13-2.25 (5H, m), 2.3-2.4 (4H, m), 2.6-2.7 (2H, m), 2.8-2.98 (2H, m), 2.98-3.10 (2H, m), 3.35-3.41 (1H, m), 3.6 (3H, s), 4.25-4.35 (1H, s), 6.9-6.70 (1H, d), 6.91-6.97 (2H, m), 7.12-7.26 (3H, m).

MS (ES+ve) 537 (M+H)+

INTERMEDIATE 28

This illustrates the preparation of 4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}cyclopentane-1,2-diol

a) 4-(4-Chloro-2-methylphenoxy)-1-(cyclopent-3-en-1-ylcarbonyl)piperidine

4-(4-Chloro-2-methylphenoxy)piperidine hydrochloride (28.6 g) and triethylamine (45.5 mL) were stirred in dichloromethane (100 mL) and cyclopent-3-ene-1-carbonyl chloride (14.26 g) in dichloromethane (100 mL) was added dropwise. When addition was complete, the reaction mixture was stirred at room temperature for 2 h. Water (250 mL) was added to the reaction mixture and product was extracted with dichloromethane. The dichloromethane was washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was filtered through a plug of silica eluting with diethyl ether to give the subtitle compound (29.5 g).

Retention Time (standard) : 2.63

MS (ES+): 320/322 $[M+H]^+$

^1H NMR $\delta_{(CDCL3)}$ 1.76 - 1.98 (4H, m), 2.21 (3H, s), 2.53 - 2.64 (2H, m), 2.69 - 2.77 (2H, m), 3.29 - 3.38 (1H, m), 3.46 - 3.54 (1H, m), 3.68 - 3.77 (3H, m), 4.49 - 4.56 (1H, m), 5.68 (2H, d), 6.75 (1H, d), 7.06 - 7.15 (2H, m)

b) 4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]carbonyl}cyclopentane-1,2-diol

4-(4-Chloro-2-methylphenoxy)-1-(cyclopent-3-en-1-ylcarbonyl)piperidine (29.5 g), N-methylmorpholine-N-oxide (37 g) and potassium osmate dihydrate (0.85 g) were stirred in a mixture of acetone (200 mL) and water (50 mL) overnight. A saturated solution of sodium metabisulphite (200 mL) was added and the mixture was stirred for 15 min. Product was extracted with dichloromethane. The dichloromethane was washed with ammonium chloride solution then with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the subtitle compound (32.0 g) as a mixture of 2 stereoisomers.

Retention Time (standard) 1.74 and 1.85min

MS (ES+) 354/356 $[M+H]^+$; base peak: 226

c) 4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}cyclopentane-1,2-diol

4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]carbonyl}cyclopentane-1,2-diol (32.0 g) was dissolved in tetrahydrofuran (100 mL) and stirred, at room temperature, under nitrogen. Borane (1 M solution in THF; 300 mL) was added dropwise and then the reaction mixture was heated under reflux for 2 h. The reaction mixture was allowed to cool slightly and methanol (60 mL) was added carefully. Heating was resumed and continued overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified using SCX resin : Non-basic impurities were eluted with methanol then product was eluted with 0.7 M ammonia in methanol. Solvent was removed *in vacuo* to give the title compound (30 g) as a mixture of 2 stereoisomers.

Retention Time (standard) 1.51

MS (ES+) 340/342 $[M+H]^+$

INTERMEDIATE 29

This illustrates the preparation of methyl (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoate

4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}cyclopentane-1,2-diol (13.18 g) was dissolved in water (85 ml). Acetic acid (2.22 ml) and sodium periodate (8.38 g) were added. The mixture was then stirred under nitrogen for 30 min. Potassium carbonate (6.97 g) was added and the solution was diluted with water and extracted into chloroform (210 ml) and then dichloromethane (2 x 120 ml). The combined extracts were washed with brine, dried over magnesium sulfate and then poured directly into a solution of methyl 4-fluoro-α-methyl-L-phenylalaninate (8.196 g), sodium triacetoxyborohydride (18.91 g) and acetic acid (2.22 ml) in dichloromethane (35 ml). The resultant mixture was stirred under nitrogen for 1 h. The solution was poured into saturated sodium bicarbonate solution (1 l). The mixture was extracted with dichloromethane (3 x 500 ml). The extracts were dried over magnesium sulfate and evaporated *in vacuo*. The crude material was purified by chromatography on neutral alumina (wetted with 5% water, 1 kg) eluting with 1:1 isohexane:ethyl acetate to give the subtitle compound (15.5 g) as an oil.

MS ESI (+ve) 517/519 $(M+H)^+$

Retention Time (fast gradient) 2.03 min.

INTERMEDIATE 30

This illustrates the preparation of methyl (2*R*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoate

Prepared following the method of Intermediate 29 using methyl 4-fluoro-α-methyl-R-phenylalaninate.

MS ESI (+ve) 517/519 $(M+H)^+$

Retention Time (fast gradient) 2.24 min.

EXAMPLE 1

This Example illustrates the preparation of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid

A solution of lithium hydroxide monohydrate (0.162 g) in water was added to a stirred solution of 2-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid methyl ester (0.52 g) in tetrahydrofuran (6 ml) and methanol (2 ml). The mixture was stirred at room temperature overnight. Ammonium acetate (3 g) in water (5 mL) was added followed by ether (10 mL). The mixture was stirred for 1 h then a white solid was collected by filtration. 100 mg was further purified by RP HPLC (gradient ammonium acetate : acetonitrile 95:5 – 5:95) to give the title compound (80 mg).

MS $[M-H]^-$ (APCI-) 521/523

Retention time (standard) 1.89

^{1}H NMR $\delta_{(CD3OD)}$: 1.15 - 1.39 (2H, m), 1.51 - 1.66 (1H, m), 1.74 - 1.88 (4H, m), 1.95 - 2.08 (2H, m), 2.25 (2H, d), 2.31 - 2.45 (7H, m), 2.64 - 2.74 (2H, m), 2.84 (1H, dd), 2.98 - 3.12 (3H, m), 3.17 (1H, dd), 4.39 - 4.49 (1H, m), 6.90 - 6.98 (3H, m), 7.23 - 7.32 (3H, m).

The following compounds were prepared from the corresponding ester using the method of Example 1:

Example	Name	MS $[M+H]^+$ (APCI+)	^1H NMR $\delta_{(CD3OD)}$
2	(2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(2-methoxyphenyl)-propanoic acid	535/537	1.15 - 1.41 (2H, m), 1.50 - 1.66 (1H, m), 1.72 - 1.88 (4H, m), 1.95 - 2.06 (2H, m), 2.25 (2H, d), 2.30 - 2.45 (7H, m), 2.63 - 2.75 (2H, m), 2.90 (1H, t), 3.02 - 3.14 (3H, m), 3.25 - 3.37 (1H, m), 3.83 (3H, s), 4.38 - 4.48 (1H, m), 6.80 (1H, t), 6.90 (2H, dd), 7.13 (1H, t), 7.22 – 7.31 (2H, m).
3	(2S)-3-(4-cyanophenyl)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-propanoic acid	530/532	1.15 - 1.36 (2H, m), 1.51 - 1.66 (1H, m), 1.74 - 1.88 (4H, m), 1.96 - 2.07 (2H, m), 2.25 (2H, d), 2.31 - 2.46 (7H, m), 2.64 - 2.74 (2H, m), 2.93 - 3.22 (5H, m), 4.39 - 4.49 (1H, m), 6.93 (1H, d), 7.29 (1H, dd), 7.47 (2H, d), 7.60 (2H, dd)
13	(2S)-2-[4-[[4-(3,4-dichloro-2-ethyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid	519/521	1.12 (3H, t), 1.16 - 1.37 (2H, m), 1.48 - 1.63 (1H, m), 1.71 - 1.86 (4H, m), 1.96 - 2.05 (2H, m), 2.23 (2H, d), 2.31 - 2.44 (4H, m), 2.63 - 2.72 (2H, m), 2.76 - 2.90 (3H, m), 2.94 - 3.03 (1H, m), 3.04 - 3.14 (2H, m), 3.18 - 3.25 (1H, m), 4.39 - 4.48 (1H, m), 6.90 (1H, d), 7.07 - 7.13 (1H, m), 7.19 (2H, t), 7.23 - 7.29 (3H, m)
14	(2S)-2-[4-[[4-(3,4-dichloro-2-ethyl-phenoxy)-1-piperidyl]methyl]-1-	537/539	1.11 (3H, t), 1.16 - 1.35 (2H, m), 1.50 - 1.62 (1H, m), 1.71 - 1.86 (4H, m), 1.96 - 2.05 (2H, m), 2.23 (2H, d), 2.30 - 2.43 (4H, m), 2.62 - 2.71 (2H, m), 2.75 -

	piperidyl]-3-(4-fluorophenyl)-propanoic acid		2.90 (3H, m), 2.95 - 3.09 (3H, m), 3.11 - 3.19 (1H, m), 4.39 - 4.47 (1H, m), 6.87 - 6.95 (3H, m), 7.22 - 7.28 (3H, m)
15	(22*S*)-2-(4-{[4-(3-chloro-4-cyano-2-methylphenoxy)-piperidin-1-yl]methyl}piperidin-1-yl)-3-phenylpropanoic acid	494/496 (M-H, ES-)	1.16 - 1.39 (2H, m), 1.51 - 1.67 (1H, m), 1.74 - 1.93 (4H, m), 2.00 - 2.11 (2H, m), 2.26 (2H, d), 2.33 (3H, s), 2.35 - 2.47 (4H, m), 2.64 - 2.73 (2H, m), 2.85 (1H, dd), 2.99 - 3.16 (3H, m), 3.23 (1H, dd), 4.57 - 4.67 (1H, m), 7.07 - 7.17 (2H, m), 7.19 - 7.31 (4H, m), 7.62 (1H, d)
16	(2*S*)-2-(4-{[4-(3-chloro-4-cyano-2-methylphenoxy)-piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-propanoic acid	514/516	1.13 - 1.32 (2H, m), 1.49 - 1.63 (1H, m), 1.74 - 1.91 (4H, m), 2.00 - 2.11 (2H, m), 2.25 (3H, d), 2.33 (3H, s), 2.37 - 2.45 (3H, m), 2.63 - 2.74 (2H, m), 2.91 - 3.08 (4H, m), 3.43 (1H, dd), 3.58 (3H, s), 4.56 - 4.66 (1H, m), 6.96 - 7.04 (2H, m), 7.09 (1H, d), 7.19 - 7.24 (2H, m), 7.61 (1H, d)
17	(2S)-2-[4-[[4-(2,4-dichloro-3-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid	523/525	1.16 - 1.39 (2H, m), 1.51 - 1.67 (1H, m), 1.74 - 1.91 (4H, m), 1.95 - 2.06 (2H, m), 2.25 (2H, d), 2.31 - 2.43 (4H, m), 2.45 (3H, s), 2.66 - 2.76 (2H, m), 2.81 - 2.89 (1H, m), 3.00 - 3.18 (4H, m), 4.42 - 4.51 (1H, m), 6.94 (3H, t), 7.24 - 7.30 (3H, m)
18	(2*S*)-2-[4-[[4-(4-chloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-	489/491	1.16 - 1.39 (2H, m), 1.50 - 1.64 (1H, m), 1.75 - 1.87 (4H, m), 1.96 - 2.07 (2H, m), 2.19 (3H, s), 2.25 (2H, d), 2.30 - 2.42 (4H, m), 2.64 - 2.74 (2H, m), 2.86 (1H, dd), 3.00 - 3.17 (4H, m), 4.35

	fluorophenyl)-propanoic acid		- 4.44 (1H, m), 6.86 - 6.97 (3H, m), 7.07 - 7.12 (2H, m), 7.24 - 7.30 (2H, m)
19	(2*S*)-2-[4-[[4-(2,4-dichloro-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid	509/511	1.16 - 1.39 (2H, m), 1.51 - 1.67 (1H, m), 1.74 - 1.91 (4H, m), 1.96 - 2.07 (2H, m), 2.26 (2H, d), 2.33 - 2.44 (4H, m), 2.66 - 2.76 (2H, m), 2.87 (1H, d), 3.06 (3H, t), 3.15 (1H, d), 4.44 - 4.54 (1H, m), 6.94 (2H, t), 7.10 (1H, d), 7.23 - 7.31 (3H, m), 7.40 (1H, dd)

EXAMPLE 4

This Example illustrates the preparation of (*S*)-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid

A mixture of methyl (*S*)-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoate (123mg), barium hydroxide (130 mg), tetrahydrofuran (2 ml), water (1 ml) and methanol (1 ml) were heated together in the microwave at 190 °C for 2.5 h. The mixture was then acidified with acetic acid (1 ml), concentrated, and purified by reverse-phase hplc (95:5 0.1% aqueous ammonium acetate/acetonitrile to 5:95 0.1% aqueous ammonium acetate/acetonitrile over 10 minutes, symmetry column to give the title compound (109 mg).

^{1}H NMR $\delta_{(CD3OD)}$ 1.00 (3H, s), 1.18 - 1.35 (2H, m), 1.48 - 1.62 (1H, m), 1.70 - 1.81 (4H, m), 1.94 - 2.04 (2H, m), 2.16 - 2.45 (6H, m), 2.71 (3H, d), 3.03 - 3.16 (2H, m), 3.23 (1H, d), 4.32 - 4.43 (1H, m), 6.89 (3H, t), 7.08 (1H, d), 7.25 (2H, t), 7.37 (1H, d).

MS (ES+ve) 523/525 $(M+H)^+$

The following compounds were prepared from the corresponding ester using the method of Example 4:

Example	Name	MS $[M+H]^+$ (APCI+)	^{1}H NMR $\delta_{(CD3OD)}$

5	(S)-2-[4-[[4-(4-chloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-2-methyl-propanoic acid	503/505	1.00 (3H, s), 1.20 - 1.36 (2H, m), 1.50 - 1.63 (1H, m), 1.71 - 1.85 (4H, m), 1.94 - 2.04 (2H, m), 2.17 (3H, s), 2.19 - 2.25 (3H, m), 2.29 - 2.44 (3H, m), 2.63 - 2.74 (3H, m), 3.03 - 3.16 (2H, m), 3.22 (1H, d), 4.33 - 4.42 (1H, m), 6.85 - 6.92 (3H, m), 7.05 - 7.10 (2H, m), 7.25 (2H, dd)
6	(S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-2-methyl-propanoic acid	537/539	1.00 (3H, s), 1.21 - 1.36 (2H, m), 1.49 - 1.63 (1H, m), 1.71 - 1.86 (4H, m), 1.95 - 2.06 (2H, m), 2.16 - 2.26 (3H, m), 2.28 - 2.44 (3H, m), 2.31 (3H, s), 2.62 - 2.75 (3H, m), 3.02 - 3.17 (2H, m), 3.22 (1H, d), 4.37 - 4.46 (1H, m), 6.85 - 6.93 (3H, m), 7.21 - 7.29 (3H, m)
12	Isomer 4 of 2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid	519/521	0.96 (3H, d), 1.15 - 1.33 (2H, m), 1.44 - 1.59 (1H, m), 1.66 - 1.82 (4H, m), 1.89 - 2.02 (2H, m), 2.08 - 2.43 (9H, m), 2.56 - 2.72 (4H, m), 3.05 (2H, d), 4.32 - 4.43 (1H, m), 6.83 - 6.91 (1H, m), 7.02 - 7.16 (3H, m), 7.17 - 7.27 (3H, m)

EXAMPLE 11

This Example illustrates the preparation of Isomer 3 of 2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-2-methyl-3-phenylpropanoic acid.

Methyl 2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-2-methyl-3-phenylpropanoate (Isomer 3; 177 mg), 6M hydrochloric acid (20 ml) and isopropyl alcohol (10 ml) were heated together at 98 °C for 22 days. The mixture was then cooled, concentrated and purified by reverse-phase hplc using 95:5 0.1% aqueous ammonium acetate/acetonitrile to 5:95 0.1% aqueous ammonium acetate/acetonitrile over 10 minutes, symmetry column, to give the title compound (38 mg).

MS $[M-H]^-$ 519/521 (APCI-)

^{1}H NMR $\delta_{(CD3OD)}$: 1.01 (3H, s), 1.24 - 1.35 (2H, m), 1.50 - 1.62 (1H, m), 1.71 - 1.87 (4H, m), 1.96 - 2.05 (2H, m), 2.15 - 2.26 (4H, m), 2.30 (3H, s), 2.32 - 2.43 (2H, m), 2.61 - 2.75 (3H, m), 3.01 - 3.18 (2H, m), 3.25 (1H, d), 4.38 - 4.46 (1H, m), 6.91 (1H, d), 7.08 - 7.29 (6H, m).

The following compounds were prepared from the corresponding ester using the method of Example 11:

Example	Name	MS $[M+H]^+$ (APCI+)	^{1}H NMR $\delta_{(CD3OD)}$
8	Isomer 1 of 2-[4-[[4-(3,4-dichlorophenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid	505/507	1.01 (3H, s), 1.17 - 1.37 (2H, m), 1.50 - 1.62 (1H, m), 1.70 - 1.82 (4H, m), 1.94 - 2.06 (2H, m), 2.15 - 2.47 (6H, m), 2.66 - 2.76 (4H, m), 3.05 - 3.18 (2H, m), 4.34 - 4.42 (1H, m), 6.88 (1H, dd), 7.07 - 7.13 (2H, m), 7.17 (2H, t), 7.25 (2H, d), 7.37 (1H, d)
9	Isomer 2 of 2-[4-[[4-(3,4-dichlorophenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid	505/507	1.01 (3H, s), 1.19 - 1.36 (2H, m), 1.50 - 1.63 (1H, m), 1.76 (4H, d), 1.95 - 2.04 (2H, m), 2.16 - 2.26 (4H, m), 2.31 (2H, t), 2.43 (1H, t), 2.65 - 2.76 (3H, m), 3.13 (2H, t), 4.34 - 4.43 (1H, m), 6.87 - 6.90 (1H, m), 7.08 - 7.13 (2H, m), 7.17 (2H, t), 7.25 (2H, d), 7.37 (1H, d)
10	(±)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-2-methyl-3-phenyl-propanoic acid	519/521	1.01 (3H, s), 1.24 - 1.35 (2H, m), 1.50 - 1.62 (1H, m), 1.71 - 1.87 (4H, m), 1.96 - 2.05 (2H, m), 2.15 - 2.26 (4H, m), 2.30 (3H, s), 2.32 - 2.43 (2H, m), 2.61 - 2.75 (3H, m), 3.01 - 3.18 (2H, m), 3.25 (1H, d), 4.38 - 4.46 (1H, m), 6.91 (1H, d), 7.08 - 7.29 (6H, m)

EXAMPLE 20

This Example illustrates the preparation of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid sodium salt

(2S)-2-[4-[[4-(3,4-Dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid (1.0 g) was suspended in methanol. Sodium hydroxide (79 mg) in water (1 ml) was added and the resulting solution was stirred for 1 h and then the solvent was evaporated. The residue was dissolved in ethanol (50 ml) at reflux and then allowed to cool. The volume was reduced to 30 ml by evaporation and the resulting solution was left to crystallise overnight. Collection of the resultant crystals gave the title compound (0.6 g).

Melting point: 227-229 °C

2.48% water by Karl Fisher analysis

^{1}H NMR $\delta_{(CD3OD)}$: 1.10 – 1.26 (2H, m), 1.43 – 1.53 (1H, m), 1.62 – 1.75 (4H, m), 1.85 – 1.95 (2H, m), 2.13 (2H, d), 2.21 (3H, s), 2.18 – 2.27 (2H, m), 2.33 (2H, t), 2.53 – 2.62 ((2H, m), 2.67 – 2.75 (1H, m), 2.86 – 2.95 (1H, m), 2.96 – 3.07 (2H, m), 3.11 – 3.17 (1H, m), 4.26 – 4.36 (1H, m), 6.81 (1H, d), 7.01 (1H, t), 7.10 (2H, t), 7.13 – 7.20 (3H, m).

EXAMPLE 21

This Example illustrates the preparation of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid sodium salt

This compound was prepared following the method of Example 20 using (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid and recrystallising by stirring with isopropanol.

Melting point: 230-232 °C.

^{1}H NMR $\delta_{(CD3OD)}$ 1.13 - 1.40 (2H, m), 1.53 - 1.68 (1H, m), 1.75 - 1.89 (4H, m), 1.96 - 2.08 (2H, m), 2.25 (2H, d), 2.31 - 2.50 (7H, m), 2.66 - 2.75 (2H, m), 2.82 (1H, dd), 2.98 - 3.15 (3H, m), 3.22 (1H, dd), 4.38 - 4.49 (1H, m), 6.91 - 7.00 (3H, m), 7.25 - 7.32 (3H, m).

EXAMPLE 22

This Example illustrates the preparation of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid potassium salt

This compound was prepared following the method of Example 20 using (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid and potassium hydroxide. The initial product from evaporation of the solvent was resuspended in methanol and evaporated and then suspended in diethyl ether and evaporated to give the title compound.

Melting point: 210-214 °C.

EXAMPLE 23

This Example illustrates the preparation of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid methanesulfonic acid salt

(2S)-2-[4-[[4-(3,4-Dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid (1.0 g) was suspended in methanol – water (3:1, 30 mL). Methanesulfonic acid (190 mg) was added and the mixture was heated under reflux until solution was obtained. The solution was cooled and the solvent was evaporated. Recrystallisation from ethanol gave the title compound (0.9 g)

Melting point: 225 – 228 °C

3.09% water by Karl Fisher analysis

^{1}H NMR $\delta_{(CD3OD)}$ 1.54 – 1.71 ((2H, m), 2.00 – 2.29 (7H, m), 2.35 (3H, s), 2.70 (3H, s), 2.98 – 3.07 (2H, m), 3.10 (2H, d), 3.23 (2H, d), 3.27 – 3.43 (4H, m), 3.53 (1H, d), 3.65 (1H, d), 3.75 – 3.84 (1H, m), 4.63 – 4.73 (1H, m), 6.96 (1H, d), 7.20 – 7.26 (1H, m), 7.26 – 7.39 (5H, m).

EXAMPLE 24

This Example illustrates the preparation of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid benzenesufonic acid salt

This compound was prepared following the method of Example 23 using benzenesulfonic acid. The salt crystallised directly on cooling the initial solution.

Melting point: 160 –162 °C

2.4% water by Karl Fisher analysis.

^{1}H NMR $\delta_{(CD3OD)}$ 1.55 – 1.71 (2H, m), 2.00 – 2.27 (7H, m), 2.34 (3H, s), 2.98 – 3.13 (4H, m), 3.23 (2H, d), 3.26 – 3.43 (4H, m), 3.52 (1H, d), 3.64 (1H, d), 3.79 (1H, t), 4.61 – 4.71 (1H, m), 6.96 (1H, d), 7.19 – 7.26 (1H, m), 7.27 – 7.35 (5H, m), 7.39 – 7.46 (3H, m), 7.81 – 7.86 (2H, m).

EXAMPLE 25

This Example illustrates the preparation of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid benzenesulfonic acid salt

This compound was prepared following the method of Example 24.

Melting point: 259-260 °C.

EXAMPLE 26

This Example illustrates the preparation of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid hydrochloride

(2S)-2-[4-[[4-(3,4-Dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-(4-fluorophenyl)-propanoic acid (0.75 g) was suspended in ether and a solution of HCl in dioxane (4M, 0.37 mL) was added. The mixture was stirred overnight and then evaporated. The residue was treated with ether and then evaporated and this procedure was repeated several times until a free-flowing solid was obtained. This solid was dried under vacuum at 50 °C overnight. The resultant solid was suspended in methanol with warming and then collected and dried to give the title compound (0.55 g)

Melting point: 281-283 °C

EXAMPLE 26

This illustrates the preparation of 2-Benzyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)butanoic acid

This compound was prepared from methyl 2-benzyl-2-(4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidin-1-yl)butanoate following the method of Example 4 to give the title compound

MS (APCI$^+$) 519/521 (M+H$^+$)

EXAMPLE 27

This illustrates the preparation of (S)-2-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-phenyl-propionic acid

Tetra-n-butylammonium hydroxide (3.12 g) was dissolved in acetonitrile (5 mL) and added to a suspension of (S)-2-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-phenyl-propionic acid methyl ester (1.0 g) in acetonitrile (9 mL) at room temperature. The mixture was stirred at this temperature for 3 h then methyl *tert*-butyl ether (10 mL) was added, followed by water (4 mL). A solution of ammonium acetate (0.89 g) in water (5 mL) was added causing the product to precipitate from solution. The mixture was stirred for 3 h at room temperature and then filtered. The filter cake was washed with water (50 mL) and methyl *tert*-butyl ether (20 mL). The product was dried under vacuum at 40 °C to give the title compound (0.88 g).

EXAMPLE 28

This illustrates the preparation of (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid (Form I)

To (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid methyl ester (1 g) in acetonitrile (9 mL) solution (Intermediate 28) was added a solution of tetra-n-butylammonium hydroxide (3.31 g, 48%w/w in water) in acetonitrile (5 mL) over 10 minutes at 20 °C.

The reaction mixture was stirred at 20-22 °C for 2 hours. Methyl-*tert*-butyl ether (10 mL) was added to the reaction mixture followed by a solution of ammonium acetate (0.87 g) in water (5 mL). After 1 h of stirring at room temperature water (5 mL) was added. The precipitate formed was stirred overnight at room temperature.

The solid was filtered and washed (slurry wash) with water (2 x 4 mL) and methyl *tert*-butylmethyl ether (6 mL). The solid was dried at 40 °C under reduced pressure

overnight to yield the title compound as a colourless solid (0.44 g; melting point 230-237 °C, starts degrading at 220 °C).

^{1}H NMR $\delta_{(CD3OD)}$ 1.25-1.40 (2H, m), 1.5-1.65 (1H, m), 1.70-1.90 (4H, m), 1.92-2.10 (2H, m), 2.20-2.25 (2H, m), 2.35 (3H, s), 2.35-2.42 (4H, m) 2.6-2.75 (2H, m), 2.78-2.90 (1H, m), 2.97-3.20 (4H, m), 4.38-4.50 (1H, m), 6.85-7.00 (3H, m), 7.20-7.30 (3H, m) MS (ES+ve) 523 (M+H)+ .

XRPD of Form I is shown in Figure 1.

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
2.2272	39.63447	50.62
2.6914	32.79941	35.64
5.3443	16.52252	1.17
7.1482	12.35663	100
8.75	10.09782	3.57
10.7172	8.24831	6.89
12.6424	6.9962	2.39
13.2608	6.67132	10.35
14.0758	6.28685	2.26
14.2953	6.19079	2.23
15.1222	5.85406	1.09
15.9917	5.53767	5.72
17.8742	4.95848	2.63
18.2983	4.8445	7.36
18.7722	4.72326	21.26
19.2498	4.60712	7.52
19.7833	4.48407	4.5
20.1738	4.39815	3.34
21.237	4.1803	2.3
22.2454	3.99304	1.4
23.3765	3.80232	2.41

24.3555	3.65165	5.04
24.6251	3.61229	5.33
25.4107	3.50236	2.98
25.9888	3.42575	1.53
26.3646	3.37776	1.87
26.8953	3.31231	1.55
31.2745	2.85777	0.79
33.0542	2.70785	1.22
34.2844	2.61345	1.18

EXAMPLE 29

This illustrates the preparation of (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid (Form II)

To (S)-{4-[4-(3,4-Dichloro-2-methylphenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluorophenyl)-propionic acid methyl ester (5 g) in acetonitrile (40 mL) was added a solution of tetra-n-butylammonium hydroxide (15.10 g, 48%w/w in water) in acetonitrile (25 mL) over 10 minutes between 10-20 °C. The reaction mixture was stirred at 20-22 °C for 2 h. To the reaction mixture was added a solution of ammonium acetate (4.35 g) in water (50 mL) forming a precipitate. A small amount of the solid was withdrawn, isolated by filtration and washed with water three times. The XRPD analysis of this solid indicated that it was form II. The slurry was then stirred overnight at room temperature. A sample of the slurry was again checked by XRPD which showed that it was now form I. The solid was filtered and washed (slurry wash) with water (3 x 20 mL). The solid was dried in the oven at 40 °C under reduced pressure overnight to yield the title compound as a colourless solid (3.60 g).

XRPD for Form II is shown in Figure 2

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
2.2315	39.55948	99.14
2.6749	33.00216	76.85
5.3589	16.47747	3.63

7.186	12.29168	100
8.6551	10.20831	1.83
10.0439	8.79962	3.1
11.0966	7.96713	1.2
12.1727	7.26509	4.68
13.1501	6.72725	14.53
14.3825	6.15345	3.85
15.1743	5.83409	2.28
17.0236	5.20427	40.99
17.3697	5.10133	64.11
18.5373	4.78257	8.87
19.1233	4.63731	67.78
19.3663	4.57968	30.28
20.0799	4.41851	6.99
21.069	4.21325	10.79
22.247	3.99275	7.08
22.8768	3.88424	3.31
24.417	3.64259	28.48
25.1834	3.53346	18.08
27.5786	3.23177	3.67
33.7683	2.6522	1.92
34.6377	2.58759	6.2
38.741	2.32245	1.74

EXAMPLE 30

This illustrates the preparation of (2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)propanoic acid

5

A Methyl (2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)propanoate

Powdered sieves (20 g, 4 Å) were added to a solution of methyl (2*R*)-3-(4-fluorophenyl)-2-hydroxypropanoate (32 g) in dichloromethane (200 mL). The mixture was stirred, under nitrogen, at room temperature, for 15 min then cooled to 0 °C. Triflic anhydride (29.9 mL) was added, followed, after 10 min, by 2,6-lutidine (41.4 mL), which was added over approximately 1 h. Stirring was continued for 1 h at 0 °C. A solution of 4-(3,4-dichloro-2-methylphenoxy)-1-(piperidin-4-ylmethyl)piperidine (57.6 g) in dichloromethane (600 mL) was added at such a rate that the internal temperature did not exceed 5 °C. Triethylamine (49.5 mL) was added dropwise and the mixture was stirred at 0 °C for 1 h. The reaction mixture was filtered through a plug of silica; washing through with dichloromethane. The filtrate was reduced in volume by evaporation under reduced pressure and then washed (x2) with water. The organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a brown oil.

B (2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)propanoic acid

A solution of lithium hydroxide monohydrate (27.0 g) in water (180 mL) was added dropwise to an ice cooled solution of methyl (2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)propanoate (from step A) in methanol (115 mL) and THF (450 mL). The mixture was stirred at room temperature overnight. A solution of ammonium acetate (165 g) in water (300 mL) was added to the reaction mixture, followed by diethyl ether (550 mL). The two phase mixture was stirred rapidly for 5.5 h then solid was collected. The solid was washed with water (2 x 300 mL) and diethyl ether (3 x 300 mL) and then dried in a vacuum oven at 40 °C overnight (batch one).

A second batch of solid was collected from the filtrate after standing for 24 h. This was similarly washed with water and diethyl ether then dried (batch two).

Lithium hydroxide monohydrate (1 eq in water) was added to a mixture of batch one in methanol and THF. The free acid was precipitated by addition of ammonium acetate in water. Once again, two crops of crystals were obtained at different time points (batches three and four). Batch three was treated with lithium hydroxide and then ammonium acetate as before to produce two further crops (batches five and six).

The lithium salt of batch two was prepared by addition of lithium hydroxide monohydrate (1eq in water). This solution was extracted with dichloromethane. A solution of ammonium acetate in water was added to the dichloromethane layer and a solid precipitated which was collected by filtration (batch seven).

Batches four, six and seven were combined and dried to give the title compound (31.19 g).

^{1}H NMR $\delta_{(CD3OD + 1 \text{ drop } NaOD)}$ 1.25 (2H, ddd), 1.50 - 1.61 (1H, m), 1.72 - 1.84 (4H, m), 1.94 - 2.02 (2H, m), 2.22 (2H, d), 2.27 - 2.40 (7H, m), 2.61 - 2.68 (2H, m), 2.82 (1H, dd), 2.99 - 3.08 (3H, m), 3.13 (1H, dd), 4.36 - 4.43 (1H, m), 6.87 - 6.95 (3H, m), 7.22 - 7.27 (3H, m).

MS 521/523 $[M-H]^-$ (APCI-)

EXAMPLE 31

This illustrates the preparation of (2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-phenylpropanoic acid

A Methyl (2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-phenylpropanoate

Powdered sieves (20 g, 4 Å) were added to a solution of methyl (2*R*)-2-hydroxy-3-phenylpropanoate (32.8 g) in dichloromethane (200 mL). The mixture was stirred, under nitrogen, at room temperature, for 15 min then cooled to 0 °C. Triflic anhydride (33.7 mL) was added, followed, after 10 min, by 2,6-lutidine (46.7 mL), which was added over approximately 1 h. Stirring was continued for 1 h at 0 °C. A solution of 4-(3,4-dichloro-2-methylphenoxy)-1-(piperidin-4-ylmethyl)piperidine (65.0 g) in dichloromethane (600 mL) was added at such a rate that the internal temperature did not exceed 5 °C. Triethylamine (55.8 mL) was added dropwise and the mixture was stirred at 0 °C for 1 h. The reaction mixture was filtered through a plug of silica; washing through with dichloromethane. The filtrate was reduced in volume by evaporation under reduced pressure and then washed (x2) with water. The organic fraction was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound as a brown oil.

B (2*S*)-2-(4-{[4-(3,4-Dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-phenylpropanoic acid

A solution of lithium hydroxide monohydrate (30.5 g) in water (180 mL) was added dropwise to an ice cooled solution of methyl (2*S*)-2-(4-{[4-(3,4-dichloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-phenylpropanoate (from step A) in methanol (115 mL) and THF (450 mL). The mixture was stirred at room temperature overnight. A solution of ammonium acetate (165 g) in water (300 mL) was added to the reaction mixture, followed by *tert*-butylmethyl ether (300 mL). The two phase mixture was stirred rapidly for 2 h. The solid was collected, washed with water (3 x 300 mL) and diethyl ether (3 x 200 mL). The solid was added to diethyl ether and stirred for 1 h then filtered. Fresh diethyl ether was added and the stirring, filtering procedure was repeated. The solid obtained was dried under vacuum at 50 °C overnight to give the title compound (33 g).

^{1}H NMR $\delta_{(CD3OD + 1 \text{ drop } NaOD)}$ 1.16 - 1.35 (2H, m), 1.50 - 1.62 (1H, m), 1.72 - 1.84 (4H, m), 1.94 - 2.03 (2H, m), 2.22 (2H, d), 2.27 - 2.39 (7H, m), 2.59 - 2.69 (2H, m), 2.85 (1H, dd), 3.01 - 3.09 (3H, m), 3.16 (1H, dd), 4.36 - 4.44 (1H, m), 6.89 (1H, d), 7.11 (1H, dt), 7.17 - 7.27 (5H, m).

MS 503/505 [M-H]- (APCI-)

EXAMPLE 32

This illustrates the preparation of (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid hydrate (Form A)

Methyl (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoate (34.5 g) and 50% aqueous hydrobromic acid (1.5 l) were heated together at 160 °C for 72 h. The hydrobromic acid was then removed *in vacuo*. The resulting solid was dissolved in a 3:1 mixture of acetonitrile : water (350 ml) and a solution of lithium hydroxide monohydrate (7 g) in water (50 ml) was added. A solution of ammonium acetate (15.42 g) in water (30ml) was then added, followed by isohexane (150 ml). The mixture was then stirred vigorously for 1 h. and allowed to stand for 1 h. The solid precipitate was collected, washed well with diethyl ether and dried overnight *in vacuo*. The solid was recrystallised from 3:1 acetontrile: water (400 ml) to give the title compound (21 g) as a channel hydrate (Form A).

3.85% water (Karl-Fischer analysis)

MS ES+ (+ve) 503/505 $(M+H)^+$

^1H NMR $\delta_{(CD3OD)}$ 1.32 (3H, s), 1.41 - 1.68 (2H, m), 1.72 - 1.84 (3H, m), 1.85 - 2.13 (4H, m), 2.15 (3H, s), 2.24 - 2.29 (2H, m), 2.31 - 2.41 (2H, m), 2.61 - 2.76 (2H, m), 2.96 - 3.09 (3H, m), 3.18 (1H, d), 3.32 - 3.40 (1H, m), 3.59 - 3.72 (1H, m), 4.30 - 4.42 (1H, m), 6.85 (1H, d), 6.96 (2H, t), 7.03 - 7.11 (2H, m), 7.23 - 7.31 (2H, m)

XRPD for Form A is shown in Figure 3

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
5.3042	16.64746	38.18
10.6081	8.33289	15.1
12.2996	7.19041	21.34
12.9368	6.83768	17.84
13.8637	6.38254	100
15.4899	5.71594	21.07
15.9475	5.55295	43.36
16.9292	5.23307	45.21
19.6122	4.52282	46.88
20.0506	4.4249	39.58
20.4452	4.34037	43.68
21.1148	4.20421	37.21
21.4664	4.13615	17.97
22.5577	3.93845	5.89
23.5073	3.78147	5.72
24.0362	3.69943	31.3
24.7697	3.59152	30.35
25.1369	3.53988	10.04
25.8045	3.4498	15.74
26.74	3.33119	9.4

27.8356	3.20251	4.01
29.399	3.03566	11.28
29.642	3.01133	11.65
31.3761	2.84874	7.22
32.3322	2.76665	7.42
33.6764	2.65923	5.23
34.41	2.6042	4.99
35.8167	2.50508	4.12

EXAMPLE 33

This illustrates the preparation of (2*R*)-2-(4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid

This was prepared following the method of Example 32 using methyl (2*R*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoate.

1H NMR $\delta_{(CD3OD)}$ 1.31 (3H, s), 1.50 (1H, q), 1.62 (1H, q), 1.73 - 1.84 (2H, m), 1.85 - 2.12 (5H, m), 2.16 (3H, s), 2.31 (2H, d), 2.35 - 2.46 (2H, m), 2.66 - 2.78 (2H, m), 2.95 - 3.11 (3H, m), 3.18 (1H, d), 3.36 (1H, d), 3.60 - 3.71 (1H, m), 4.33 - 4.43 (1H, m), 6.86 (1H, d), 6.96 (2H, t), 7.03 - 7.11 (2H, m), 7.26 (2H, t)

MS (ES-ve) 501/503 $(M-H)^+$

EXAMPLES 34

(2*S*)-2-(4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid Form B

(2*S*)-2-(4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid (for example amorphous or crystalline) can initially be partly dissolved in an organic solvent and stirred until Form B is obtained. The process involves a solution mediated transformation in the slurry without complete dissolution of the starting material. This transformation is thermodynamically driven to yield a more stable form with a lower solubility under the conditions evaluated.

Form B is typically formed when a slurry of Form A of (2S)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid is stirred in ethanol at 25 °C or 60 °C for greater than 1 day.

XRPD for (2*S*)-2-(4-{[4-(4-Chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid ethanol solvate Form B is shown in Figure 4

Pos. [°2Th.]	d-spacing [Å]	Rel. Int. [%]
7.6772	11.50625	32.02
8.9078	9.91929	3.67
13.307	6.64824	100
13.7582	6.43123	6.47
15.2087	5.82096	32.61
15.4305	5.73779	15.65
16.3607	5.41362	6.19
17.3791	5.09859	18.01
18.3842	4.82206	71.89
19.6742	4.5087	87.16
20.0571	4.42348	6.95
20.6439	4.29904	13.54
21.6962	4.09284	43.29
22.7189	3.91087	19.79
23.0611	3.85361	8.87
24.3742	3.6489	5.79
26.3108	3.38455	2.6
26.7429	3.33083	4.82
29.037	3.07268	1.93
29.8487	2.99095	1.32
32.0179	2.79309	2.41

EXAMPLE 35

Histamine H1 receptor binding activity of compounds of the invention was assessed by competition displacement of 1nM [3H]-pyrilamine (Amersham, Bucks, Product code TRK 608, specific activity 30Ci/mmol) to 2μg membranes prepared from recombinant CHO-K1 cells expressing the human H1 receptor (Euroscreen SA, Brussels, Belgium, product code ES-390-M) in assay buffer (50mM Tris pH 7.4 containing 2mM $MgCl_2$, 250mM sucrose and 100mM NaCl) for 1 hour at room temperature.

The following compounds of the invention gave inhibition of [3H] pyrilimine binding:

Example	H1 pKi
3	7.5
4	7.1
6	7.5
13	7.0

EXAMPLE 36

Eotaxin-2-induced shape change in eosinophils in human blood *in vitro*

See for example, Differential regulation of eosinophil chemokine signaling via CCR3 and non-CCR3 pathways. Sabroe I, Hartnell A, Jopling LA, Bel S, Ponath PD, Pease JE, Collins PD, Williams TJ. J Immunol. 1999 Mar 1;162(5):2946-55.

Human blood, collected by venous puncture into 9 mL lithium-heparin tubes, was incubated with the CCR3 agonist eotaxin-2 in the presence of vehicle (0.1% (v/v) DMSO) or test compound for 4 min at 37°C in a deep, 96-square-well plate. The blood was fixed with Optilyse B (100 μL) at room temperature for 10 min and then the red blood cells were lysed with distilled water (1 mL) for 60 min at room temperature.

The plate was centrifuged at room temperature for 5 min at 300 g. The pellet was re-suspended in assay buffer (PBS without $CaCl_2$ and $MgCl_2$, containing HEPES (10 mM), Glucose (10 mM) and 0.1% (w/v) BSA, pH 7.4)) and the samples were analysed using flow cytometry (FC500, Beckman Coulter). The high autofluorescence of eosinophils allowed them to be identified as a discrete population from the other blood cell types. Eosinophil shape was monitored as the refractive index of the eosinophil population as determined using the forward scatter signal in flow cytometry.

Eotaxin-2 induced a concentration-dependent change in the forward scatter of eosinophils and these data were used to construct a concentration effect curve (E/[A] curve). The rightward displacement of the eotaxin-2 E/[A] curve in the presence of a CCR3 antagonist was used to estimate a pA_2 value in blood using the following equation:

$$\text{Single } pA_2 = -\log_{10}([B] / (r-1))$$

where r is the ratio of the concentrations required for half maximal effects of eotaxin-2 in the absence and presence of antagonist ($[A]_{50}$ for eotaxin-2 in the presence of antagonist divided by $[A]_{50}$ for control eotaxin-2 curve) and [B] is the molar concentration of antagonist.

The following compounds of the invention gave inhibition of shape-change:

Example	CCR3 pA_2
1	7.3
2	7.7
3	7.7
4	7.6
5	7.9
6	8.2
12	8.0
13	6.7
14	6.7
16	7.1
20	7.2
21	7.3
22	7.3
23	7.2
24	7.2
25	7.3
26	7.3

EXAMPLE 37

Determination Of Compound Affinity At Human Recombinant CCR3 Receptors Assessed By Competition Of [^{3}H]-4-(2,4-dichloro-3-methylphenoxy)-1'-[4-(methylsulfonyl)benzoyl]-1,4'-bipiperidine for CHO-K1 Cell Membranes *In Vitro*

Membranes, prepared from CHO-K1 cells stably expressing recombinant human CCR3, suspended in assay buffer (50 mM Tris-Base, pH 7.4; containing sodium chloride (100mM) and magnesium chloride (2 mM)) were incubated in the presence of 2 nM [^{3}H]-4-(2,4-dichloro-3-methylphenoxy)-1'-[4-(methylsulfonyl)benzoyl]-1,4'-bipiperidine, along with vehicle (1 % (v/v) DMSO), 4-(4-chloro-3-methylphenoxy)-1'-[2-(methylsulfonyl)benzoyl]-1,4'-bipiperidine (to define non-specific binding) or test compound for 2 h at 37 °C in round bottomed 96-well plates. The plates were then filtered onto GF/B filter plates, pre-soaked for 1 hour in plate-coating solution (0.3% (w/v) polyethylenimine, 0.2% (w/v) BSA in de-ionised water), using a 96-well plate Tomtec cell harvester. Four washes (250 µL) with wash buffer (50 mM Tris-Base, pH 7.4 containing sodium chloride (500 mM) and magnesium chloride (2 mM)) were performed at 4 °C to remove unbound radioactivity. Plates were dried and MicroScint-O (50 µL) was added to each well. The plates were sealed (TopSeal A) and filter-bound radioactivity was measured with a scintillation counter (TopCount, Packard BioScience) using a 1 minute counting protocol.

Specific binding was determined from values of the control wells minus the values for the NSB wells for each assay plate. pIC_{50} values were calculated using a four parameter logistic fit (where pIC_{50} is defined as the negative logarithm of the concentration of compound required for 50% reduction in specific [^{3}H]- 4-(2,4-dichloro-3-methylphenoxy)-1'-[4-(methylsulfonyl)benzoyl]-1,4'-bipiperidine binding). Data were presented as mean pKi values (calculated by applying a Cheng-Prussof correction to pIC_{50} values) from a minimum of 2 separate experiments.

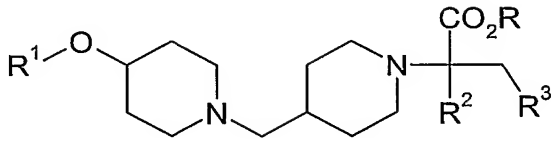
The following compounds of the invention gave inhibition of binding:

Example	CCR3 pKi
1	9.3
2	9.2
3	9.3

4	9.1
5	9.2
6	9.7
8	7.6
9	8.6
10	8.3
11	8.8
12	9.7
13	8.9
14	9.3
15	8.2
16	8.9
17	9.3
18	8.4
19	8.3
20	8.7
21	9.3
22	9.3
23	8.7
24	8.7
25	9.3
26	9.3

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl or C_{1-4} alkoxy;

R^2 is methyl or ethyl;

R is hydrogen, or CO_2R is $(CO_2^-)_pR^{p+}$ wherein R^{p+} is a univalent cation or two carboxylates may coordinate a divalent cation;

p is 1 or 2;

R^3 is phenyl optionally substituted with halogen, cyano, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3 or OCF_3;

when R^1 is 2-methyl-3,4-dichlorophenyl and R^3 is 4-fluorophenyl, 4-cyanophenyl or 2-methoxyphenyl, then R^2 can also be hydrogen;

or a N-oxide thereof; or a pharmaceutically acceptable salt thereof.

2. A salt of (2S)-2-[4-[[4-(3,4-dichloro-2-methyl-phenoxy)-1-piperidyl]methyl]-1-piperidyl]-3-phenylpropanoic acid, provided it is not the dihydrochloride salt.

3. A salt as claimed in claim 2 which is a methanesulfonate or benzenesulfonate salt.

4. A compound as claimed in claim 1 wherein R^2 is methyl.

5. A compound as claimed in claim 1 or 4 wherein R^1 is phenyl optionally substituted by chloro and methyl.

6. A compound as claimed in claim 5 wherein R^1 is 2-methyl-4-chloro-phenyl.

7. A compound as claimed in claim 5 wherein R^1 is 2-methyl-3,4-dichlorophenyl.

8. A compound as claimed in claim 1, 4, 5 or 6 wherein R^3 is 4-fluorophenyl.

9. A compound as claimed in claim 1, 4, 5, 6, 7 or 8 wherein R is hydrogen.

10. The compound (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid, or a pharmaceutically acceptable salt thereof.

11. A pharmaceutically acceptable salt of (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid which is a sodium, potassium or $(CH_2CH_2OH)_3NH^+$ salt, or a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, fumarate, maleate, malonate, succinate, tartrate, citrate, oxalate, methanesulfonate, benzenesulfonate or *p*-toluenesulfonic acid salt.

12. The compound (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid.

13. A polymorph of (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid hydrate (Form A) having an X-ray powder diffraction pattern containing specific peaks at: 5.3 (±0.1°), 10.6 (±0.1°), 12.3 (±0.1°), 12.9 (±0.1°), 13.9 (±0.1°), 15.5 (±0.1°), 15.9 (±0.1°), 16.9 (±0.1°), 19.6 (±0.1°), 20.0 (±0.1°), 20.4 (±0.1°), 21.1 (±0.1°), 21.5 (±0.1°), 24.0 (±0.1°), 24.8 (±0.1°), 25.1 (±0.1°), 25.8 (±0.1°), 29.4 (±0.1°) and 29.6 (±0.1°) 2θ.

14. A polymorph of (2*S*)-2-(4-{[4-(4-chloro-2-methylphenoxy)piperidin-1-yl]methyl}piperidin-1-yl)-3-(4-fluorophenyl)-2-methylpropanoic acid ethanol solvate (Form B) having an X-ray powder diffraction pattern containing specific peaks at: 7.7 (±0.1°), 13.3 (±0.1°), 15.2 (±0.1°), 15.4 (±0.1°), 17.4 (±0.1°), 18.4 (±0.1°), 19.7 (±0.1°), 20.6 (±0.1°), 21.7 (±0.1°) and 22.7 (±0.1°) 2θ.

15. A compound as claimed in claim 1 wherein R^1 is 2-methyl-3,4-dichlorophenyl, R^2 is hydrogen, and R^3 is 4-fluorophenyl

16. The compound (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid, or a pharmaceutically acceptable salt thereof.

17. A pharmaceutically acceptable salt of (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid which is a sodium, potassium or $(CH_2CH_2OH)_3NH^+$ salt, or a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, fumarate, maleate, malonate, succinate, tartrate, citrate, oxalate, methanesulfonate, benzenesulfonate or *p*-toluenesulfonic acid salt.

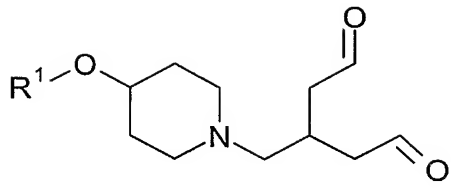
18. The compound (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid.

19. A polymorph of (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid (Form I) having an X-ray powder diffraction pattern containing specific peaks at: 2.2 (±0.1°), 2.7 (±0.1°), 7.1 (±0.1°), 10.7 (±0.1°), 13.3 (±0.1°) and 18.8 (±0.1°) 2θ.

20. A polymorph of (S)-{4-[4-(3,4-dichloro-2-methyl-phenoxy)-piperidin-1-ylmethyl]-piperidin-1-yl}-3-(4-fluoro-phenyl)-propionic acid (Form II) having an X-ray powder diffraction pattern containing specific peaks at: 2.2 (±0.1°), 2.67 (±0.1°), 7.2 (±0.1°), 13.2 (±0.1°), 17.0 (±0.1°), 17.4 (±0.1°), 19.1 (±0.1°), 19.4 (±0.1°), 21.1 (±0.1°), 24.4 (±0.1°) and 25.2 (±0.1°) 2θ.

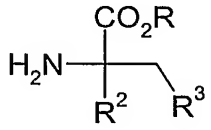
21. A processes for preparing a compound as claimed in claim 1, the process comprising:

a. reacting a compound of formula (II):



(II)

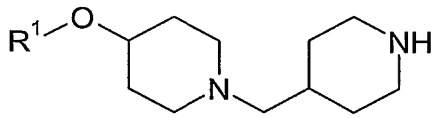
with a compound of formula (III):



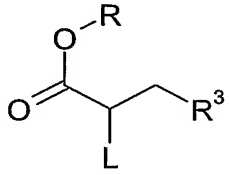
(III)

wherein R is alkyl, in the presence of $NaBH(OAc)_3$ or $NaBH_3(CN)$ in a suitable solvent, at a suitable temperature, and subsequently hydrolysing the ester; or,

b. when R^2 is H, reacting of a compound of formula (V) with a compound of formula (VI):



(V)



(VI)

wherein R is alkyl and L is a suitable leaving group, in a suitable solvent, at a temperature in the range 0 – 30 °C, and in the presence of a base; and subsequently hydrolysing the ester.

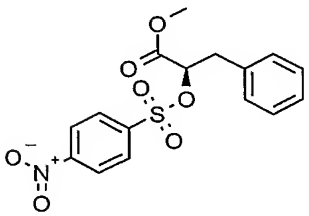
22. A pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in claim 1, or a salt as claimed in claim 2, and a pharmaceutically acceptable adjuvant, diluent or carrier.

23. A compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in claim 1, or a salt as claimed in claim 2, for use in therapy.

24. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in claim 1, or a salt as claimed in claim 2, in the manufacture of a medicament for use in therapy.

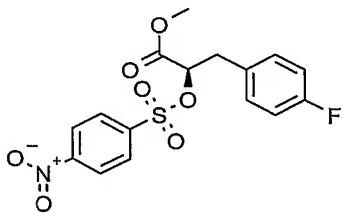
25. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof as claimed in claim 1, or a salt as claimed in claim 2.

26. An intermediate compound of formula:



(R)-2-(4-nitro-benzenesulfonyloxy)-3-phenyl-propionic acid methyl ester

or



(R)-3-(4-fluoro-phenyl)-2-(4-nitro-benzene-sulfonyloxy)-propionic acid methyl ester

Figure 1

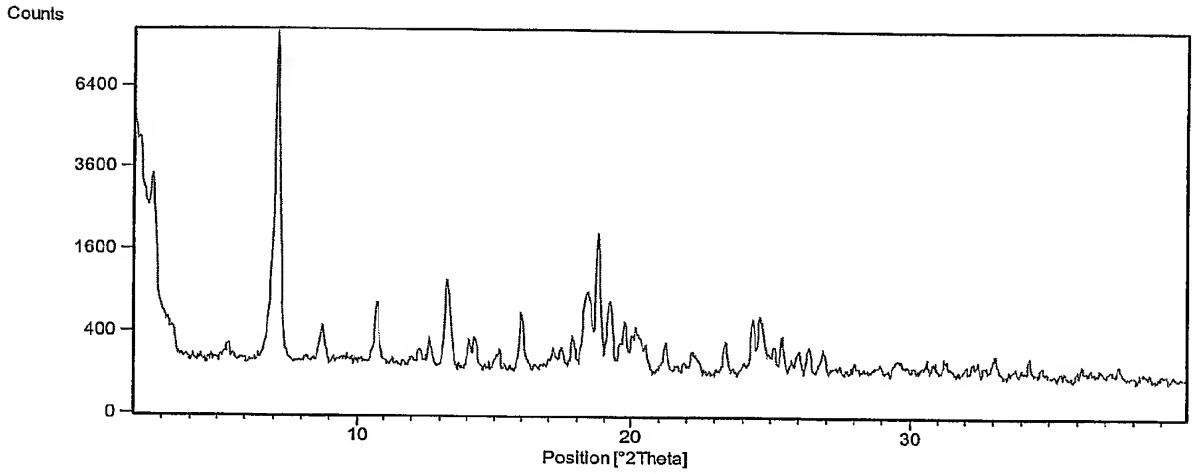


Figure 2

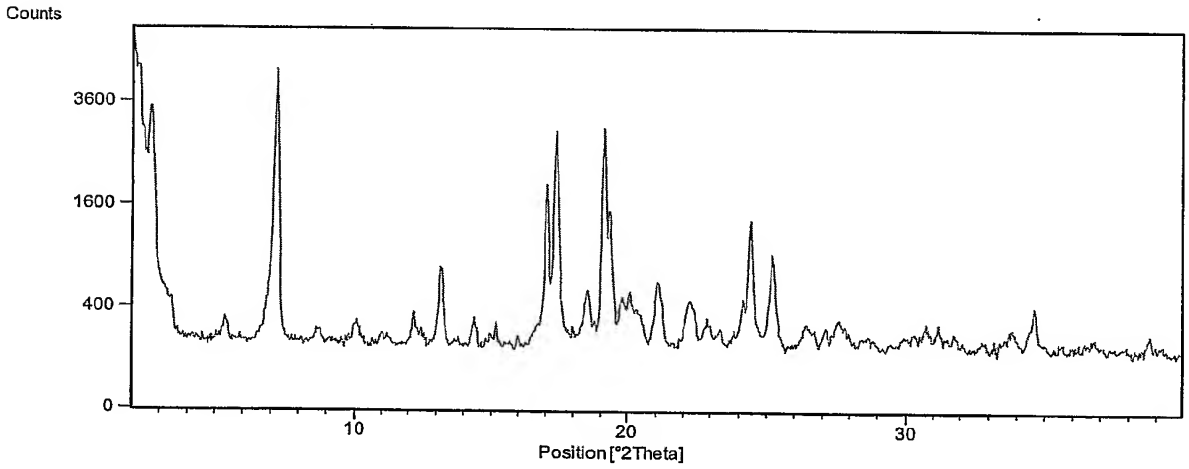


Figure 3

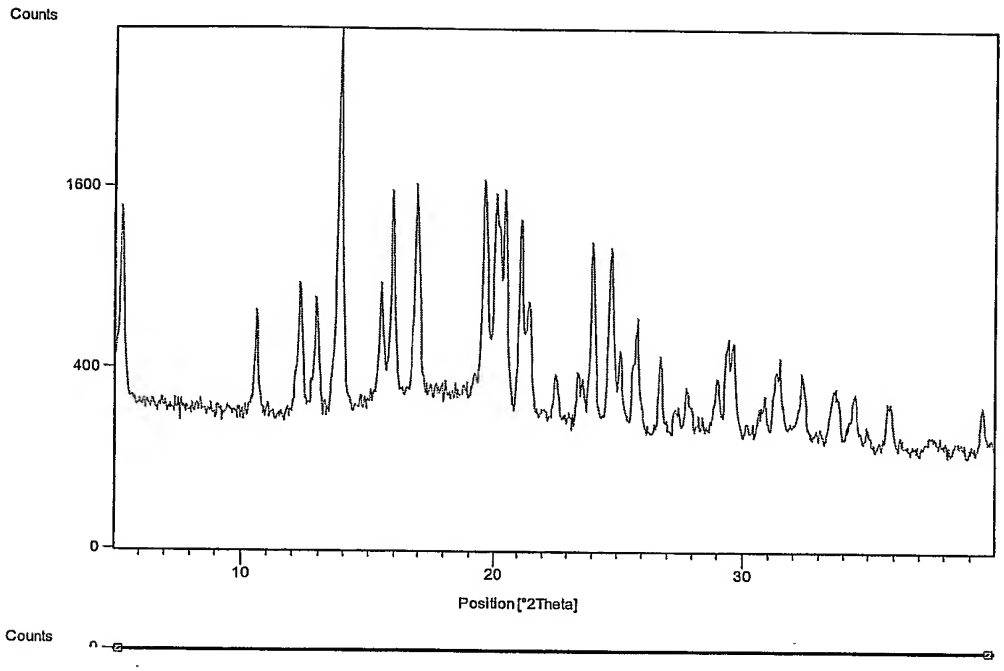
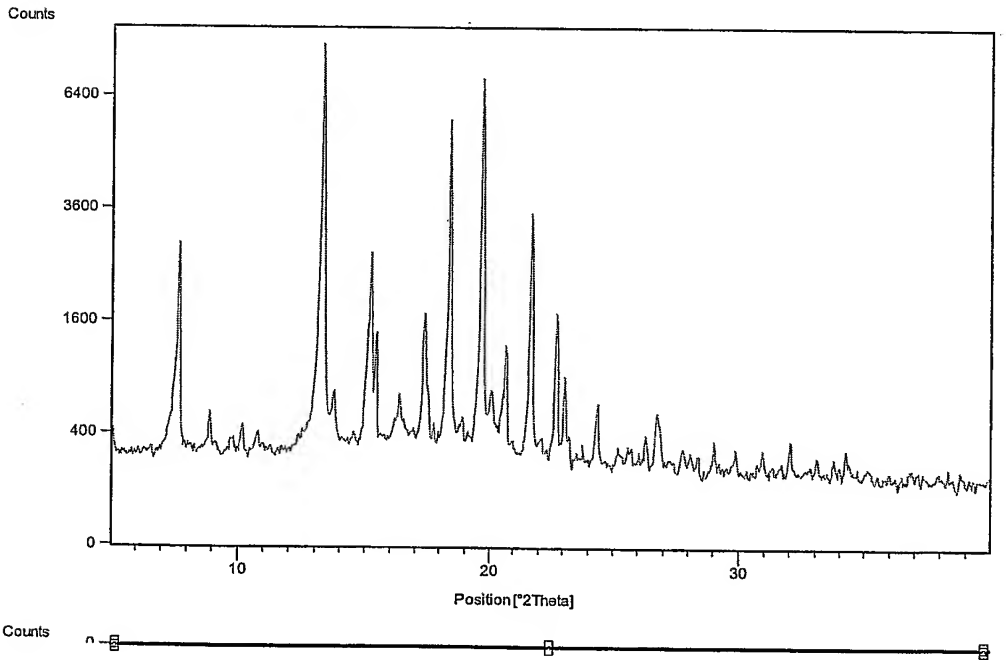


Figure 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE06/000893

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 25 relates to a method of treatment of the human or animal body by surgery or by therapy /Rule 39.1(iv). Nevertheless, a search has been carried out for this claim, based on the alleged effects of the product.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1: Claims 1-25 directed to compounds of formula I, their preparation and pharmaceutical compositions thereof as well as their medical use.

2: Claim 26 directed to intermediates.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000893

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004087659 A1 (ASTRAZENECA AB), 14 October 2004 (14.10.2004)	1-25
A	WO 2004029041 A1 (ASTRAZENECA AB), 8 April 2004 (08.04.2004)	1-25
A	ROBERT V. HOFFMAN et al: "THE PREPARATION OF 2-HYDRAZINYL ESTERS IN HIGH OPTICAL PURITY FROM 2-SULFONYLOXY ESTERS" Tetrahedron Letters, Vol. 31, No. 21, page 2953-2956, 1990; compound C, page 2953; compound C, page 2954	26

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 November 2006	28-11-2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/MP Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (April 2005)

International application No.
PCT/SE06/000893

International patent classification (IPC)

C07D 211/46 (2006.01)
A61K 31/4545 (2006.01)
A61P 11/00 (2006.01)
A61P 19/02 (2006.01)
A61P 29/00 (2006.01)
A61P 37/00 (2006.01)
C07C 309/73 (2006.01)

Download your patent documents at www.prv.se
The cited patent documents can be downloaded at www.prv.se by following the links:

- In English/Searches and advisory services/Cited documents (service in English) or
- e-tjänster/anförda dokument (service in Swedish).

Use the application number as username.
The password is **BNYMLHJKZN**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

WO	2004087659	A1	14/10/2004	AU	2003239002	A	00/00/0000
				AU	2004226010	A	14/10/2004
				BR	PI0409069	A	28/03/2006
				CA	2521073	A	14/10/2004
				CN	1768037	A	03/05/2006
				EP	1512313	A	09/03/2005
				EP	1620400	A	01/02/2006
				JP	2006522113	T	28/09/2006
				MX	PA05010374	A	17/11/2005
				NO	20055068	A	02/01/2006
				RU	2005128793	A	10/05/2006
				SE	0300957	D	00/00/0000
				US	20060124635	A	15/06/2006
WO	2004029041	A1	08/04/2004	AU	2003259004	A	00/00/0000
				BR	0314688	A	02/08/2005
				CA	2497280	A	08/04/2004
				CN	1684952	A	19/10/2005
				EP	1546130	A	29/06/2005
				JP	2006503066	T	26/01/2006
				MX	PA05003007	A	22/06/2005
				NO	20051965	A	23/06/2005
				RU	2005105053	A	10/12/2005
				SE	0202838	D	00/00/0000
				US	20060040984	A	23/02/2006
				ZA	200502341	A	19/09/2005